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imum intensity of the cardiac impulse, the outline of the superficial area of cardiac dulness; the description of adventitious sounds, if any were found; the character of the diastolic sounds, the character of the muscular quality of the systolic sound; the extent of the superficial area of liver dulness, observations of the blood-pressure, and the rate and character of the pulse. Early in the course of the routine examinations I located the borders of cardiac dulness and the point of maximum impulse with relation to the midclavicular line. Later I located these points with reference to the midsternal line, measuring the distance from that line in inches. At the beginning of my routine examinations I made no attempt to record the size of the area of cardiac dulness, later I began to record the transverse diameter of this area in inches, and still later I recorded the oblique diameter of this area in inches. The oblique diameter was measured from the point of junction of the right border with the upper border of cardiac dulness, to the point of maximum impulse.

The blood-pressure observations were all made in the recumbent posture. The cuff was always applied next to the skin of the arm. A Stanton sphygmomanometer was always used. The auscultatory method of determining blood-pressure was always used. The systolic pressure was recorded as the point at which the first tap was heard. The diastolic pressure was recorded as the point at which the tap disappeared.

The details of the method of administering the baths will be found in a paper which I read before the Medical Society of the State of New York in 1911.<sup>4</sup>

In the case of a male patient (Case 1) aged 76 years, who was suffering from fibroid myocarditis, blood-pressure observations were made just before entering the bath tub, immediately after the bath was given, and after one hour's rest in the recumbent posture. The accompanying table (Table 1) gives the details of these observations.

Before the first bath the patient's systolic pressure was 142 mm, before the last bath in the series his systolic pressure was 135 mm, and an hour after the last bath his systolic pressure was 154 mm. The accompanying chart (Chart 1) of the fluctuations of the systolic pressure indicates that the tendency of the pressure during the course of treatment was upward.

The usual train of circumstances in this case was to find that the systolic pressure was higher immediately after the bath than it was before the bath was given, and after the hour's rest to find it lower than it was before the bath was given. This train of events followed in ten instances.

At the sixth bath the systolic pressure was the same after the bath as it was before, an hour after the bath there was a drop of 22 mm.

At the ninth bath the systolic pressure after the treatment was 2 mm lower than it was before, and one hour after the treatment it was the same as it was immediately after.

<sup>4</sup> Swan. New York State Jour. Med., August, 1911, vi, 373.

At the eleventh bath the systolic pressure immediately after the treatment was 5 mm higher than it was before. After the hour's rest it was 1 mm higher than it was immediately after the bath.

After the twelfth bath the pressure fell 3 mm and after the hour's rest it had risen 8 mm. At the fourteenth bath the systolic pressure was 6 mm higher immediately after than it was before the bath was given. After an hour's rest it was 7 mm higher than it was immediately after the bath was given. At the eighteenth bath the systolic pressure rose 18 mm and after an hour's rest it rose 1 mm.

The immediate effect of the bath was to raise the pressure fourteen times, to lower it twice, and no effect was noted once. The observations at the fourth bath were unfortunately missed. The increases of systolic pressure immediately after the baths amounted to 2 mm, 3 mm, 11 mm,

TABLE 1—FIBROID MYOCARDITIS BLOOD PRESSURE OBSERVATIONS

No of Bath	B P Before Bath				B P After Bath				B P One Hour After Bath			
	S *	D	M	PP	S.	D	M	PP	S	D	M	PP
1	142	85	113 5	57	144	80	112	64	137	85	111	52
2	145	85	115	60	148	85	116 5	63	139	90	114 5	49
3	137	86	111 5	51	148	83	115 5	65	135	90	112 5	45
4†												
5	142	90	116	52	158	92	125	66	138	92	115	46
6	145	82	113 5	63	145	85	115	60	123	75	99	48
7	138	78	108	60	154	82	118	72	148	83	115 5	67
8	144	82	113	62	160	83	121 5	77	149	85	117	64
9	157	78	117 5	79	155	84	119 5	71	155	82	118 5	73
10	125	70	97 5	55	148	82	115	66	135	80	107 5	55
11	125	97	111	28	130	77	103 5	53	131	75	103	56
12	140	95	117 5	45	137	95	116	42	145	88	116 5	57
13	130	83	106 5	47	138	78	108	60	†			
14	149	92	120 5	57	155	82	118 5	73	162	85	123 5	77
15	150	86	118	64	158	86	122	72	147	91	119	76
16	143	80	111 5	63	165	95	130	70	148	84	116	64
17	134	80	107	54	145	78	111 5	67	142	82	112	60
18	135	80	107 5	55	153	80	116 5	73	154	84	119	70

\*S, systolic, D, diastolic, M, mean pressure, PP, pulse pressure

†Observations missed

16 mm, 16 mm, 16 mm, 23 mm, 5 mm, 8 mm, 6 mm, 8 mm, 22 mm, 11 mm and 18 mm, respectively, an average of 11.7 mm at each treatment. The decreases of the systolic pressure amounted to 2 mm after one bath and 3 mm after the other.

After the hour's rest the systolic pressure was higher in nine instances and lower in seven than it was before the bath was given. The observation one hour after the thirteenth bath was unavoidably missed. The increases of the systolic pressure an hour after the bath amounted to 10 mm, 5 mm, 10 mm, 6 mm, 5 mm, 13 mm, 5 mm, 8 mm, 19 mm, respectively, an average of 9 mm at each treatment. The decreases of the systolic pressure one hour after each bath amounted to 5 mm, 6 mm, 2 mm, 1 mm, 22 mm, 2 mm, 3 mm, respectively, an average of 6.2 mm for each treatment.

At the beginning of the course of treatment the patient's pulse-pressure was 57, before the last bath his pulse-pressure was 55, immediately after the bath it was 73; and after an hour's rest it was 70

The usual train of events in relation to the pulse-pressure was to have a well-marked elevation immediately after the treatment and a depression after the hour's rest. This train of circumstances followed eleven of the treatments. At the sixth bath the pulse-pressure was 3 mm lower immediately after the treatment and 12 mm lower after the hour's rest.

At the ninth bath the pulse-pressure was 8 mm lower immediately after the treatment and after the hour's rest it had increased 2 mm.

At the eleventh bath there was an elevation of pulse-pressure of 25 mm immediately after the bath, and after the hour's rest there was a further elevation of 3 mm.

After the twelfth bath the pulse-pressure was depressed 3 mm immediately and there was an elevation of 15 mm after the hour's rest.

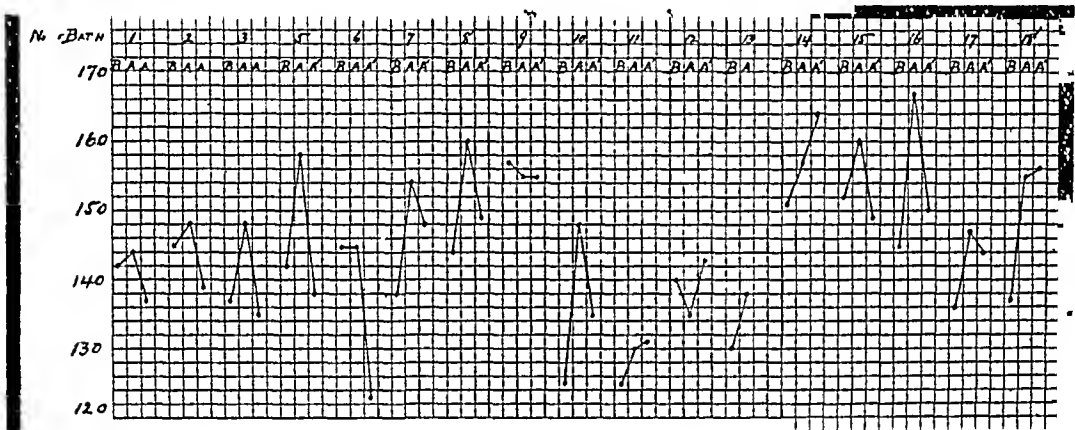


Chart 1—Systolic blood-pressure curve. Carbonated brine baths. Fibroid myocarditis. B = Immediately before the bath. A = Immediately after the bath. A' = One hour after the bath. The observations at the fourth bath and the observation one hour after the thirteenth bath were missed.

Immediately after the bath the pulse-pressure was elevated fourteen times and lowered three times. The elevations amounted to 7 mm, 3 mm, 14 mm, 12 mm, 15 mm, 11 mm, 25 mm, 13 mm, 16 mm, 8 mm, 7 mm, 13 mm, 18 mm, respectively, an average of 12.5 mm for each treatment. The lowering of the pulse-pressure amounted to 3 mm, 8 mm and 3 mm, respectively, an average of 4.6 for each treatment.

An hour after the bath the pulse-pressure was elevated eight times, lowered seven times and was unchanged once. The elevations in pulse-pressure amounted to 5 mm, 2 mm, 28 mm, 12 mm, 20 mm, 1 mm, 6 mm and 15 mm, respectively, an average of 11.1 mm for each treatment. The depressions of pulse-pressure amounted to 5 mm, 11 mm, 6 mm, 5 mm, 15 mm, 6 mm and 8 mm, respectively, an average of 8.1 mm for each treatment.



In this patient the systolic pressure on admission was 142 mm, and during the course of his treatment it increased to 165 mm on one occasion, and was above 150 mm on thirteen occasions. The highest increase of systolic pressure at any one treatment was 23 mm.

He had an hypertrophied heart and a fibroid myocarditis. He had a pulse of normal rate, of good strength and volume, and an artery which was recorded as not palpable at the beginning of the treatment and palpable at its close. It may be supposed that in this patient the fibroid changes in the heart-muscle had increased much faster than the thickening of the walls of the peripheral vessels.

The danger of administering a form of treatment capable of producing an elevation of the systolic pressure of 22 and 23 mm, and of 25 to 28 mm of the pulse-pressure to an individual with thickened and rigid arteries is not, in my opinion, altogether theoretical.

TABLE 2—PARENCHYMATOUS MYOCARDITIS BLOOD-PRESSURE OBSERVATIONS

No. of Bath	B P Before Bath				B P After Bath				B P One Hour After Bath						
	S *	P	D	M	PP	S	P	D	M	PP	S	P	D	M	PP
1	107	55		80.5	52	114	55		84.5	59	112	58		85	54
2	114	60		87	54	112	58		85	54	110	58		84	52
3	118	55		86.5	63	112	60		86	52	120	62		91	58
4	107	58		82.5	49	111	62		86.5	49	106	47		76.5	59
5	111	55		83	56	107	64		85.5	43	109	55		82	54
6	114	55		84.5	59	113	58		85.5	55	114	54		84	60
7	110	63		86.5	47	111	68		89.5	43	113	65		89	48
8	112	58		85	54	113	65		89	48	117	70		93.5	47
9	110	52		81	58	110	60		85	50	113	60		86.5	53
10	114	45		79.5	69	115	50		82.5	65	107	48		77.5	59
11	106	53		79.5	53	110	58		84	52	112	55		83.5	57
12	114	54		84	60	117	60		88.5	57	117	57		87	60
13	108	64		86	44	116	70		90	46	114	70		92	44
14	115	75		95	40	120	65		92	55	114	80		97	34
15	109	60		84	49	110	70		90	40	114	83		98	31
16	115	55		85	60	110	60		85	50	115	55		85	60
17	104	57		80.5	47	112	64		88	48	106	65		85.5	31
18	106	64		85	42	113	64		88.5	49	113	64		88.5	49

In the case of a female aged 26 years (Case 16), who was suffering from parenchymatous myocarditis, the observations made before, after, and one hour after the bath are given in Table 2.

In this case there was usually an elevation of systolic pressure (Chart 2) immediately after the bath, and at the end of the hour's rest the systolic pressure was usually higher than it was before the bath was given although often lower than immediately after the treatment.

Immediately after the bath the systolic pressure was elevated eleven times reduced six times and was unchanged once. The elevations of pressure amounted to 7 mm, 4 mm, 1 mm, 1 mm, 4 mm, 3 mm, 8 mm, 5 mm, 1 mm, 8 mm and 7 mm respectively, an average of 4.2 mm for each treatment. The reductions of systolic pressure amounted to

2 mm, 6 mm, 4 mm, 1 mm, 1 mm and 5 mm, respectively, an average of 3.1 for each treatment

One hour after the bath the systolic pressure was raised eleven times, reduced five times, and unchanged twice. The elevations amounted to 5 mm, 2 mm, 3 mm, 5 mm, 3 mm, 6 mm, 3 mm, 6 mm, 5 mm, 2 mm and 7 mm, respectively, an average of 4.2 mm at each treatment.

The reductions of systolic pressure amounted to 4 mm, 1 mm, 2 mm, 7 mm and 1 mm, respectively, an average of 3 mm for each treatment.

The influence on the pulse-pressure in this case was usually a decrease in the pressure immediately after the treatment, followed by an elevation after an hour's rest after half the treatments, and a depression after the other half. The pulse-pressure was 3 mm lower at the conclusion of the series than it was at the beginning. Immediately after the baths the pulse-pressure was elevated five times, reduced eleven times, and no change was noted twice. The elevations amounted to 7 mm, 2 mm, 15 mm, 1 mm and 7 mm, respectively, an average elevation of 6.3 mm after each treatment. The reductions in pressure amounted to 11 mm,

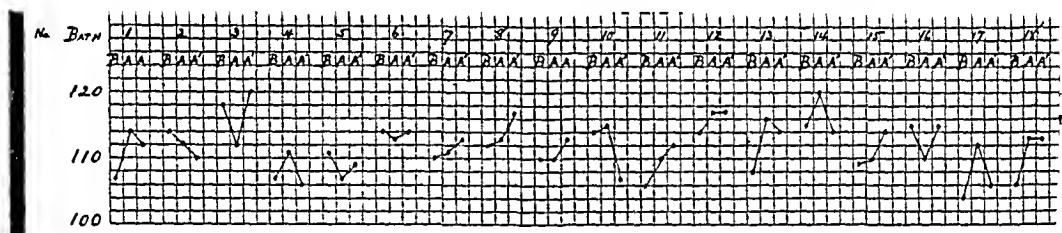


Chart 2—Systolic blood-pressure curve. Carbonated bime baths. Parenchymatous myocarditis. B = Immediately before the bath. A = Immediately after the bath. A' = One hour after the bath.

13 mm, 4 mm, 4 mm, 6 mm, 8 mm, 4 mm, 1 mm, 3 mm, 9 mm and 10 mm, respectively, an average of 6.6 mm for each treatment.

After the hour's rest the pulse-pressure was raised six times, lowered nine times, and no change was noted three times. The elevations of the pulse-pressure above that recorded before the bath was given amounted to 2 mm, 10 mm, 1 mm, 1 mm, 4 mm and 7 mm, respectively, an average elevation of 4.1 mm at each treatment.

The reductions in pulse-pressure after the hour's rest amounted to 2 mm, 5 mm, 2 mm, 7 mm, 5 mm, 10 mm, 6 mm, 18 mm and 6 mm, respectively; an average of 6.7 mm after each treatment.

In the case of a female aged 20 years (Case 3), who was suffering from mitral regurgitation with beginning loss of compensation, observations were made before the baths and immediately after the baths (Table 3). The observations in connection with the ninth, twelfth, fifteenth and sixteenth baths were missed.

Immediately after the first bath there was an increase of 38 mm in the systolic pressure. The systolic pressure was increased six times,

reduced six times, and was unchanged twice The increase of systolic pressure amounted to 38 mm , 8 mm , 3 mm , 3 mm , 4 mm and 6 mm , respectively, an average increase of 10 3 mm at each bath The reductions of systolic pressure amounted to 34 mm , 12 mm , 2 mm , 6 mm , 10 mm and 6 mm , respectively, an average decrease of 11 6 mm at each bath

The pulse-pressure was raised seven times, lowered five times, and no change was observed twice The elevations of pulse-pressure amounted to 16 mm , 11 mm , 5 mm , 3 mm , 3 mm , 3 mm and 2 mm , respectively, an average elevation of 6 1 mm at each treatment

The reductions of the pulse-pressure amounted to 12 mm , 24 mm , 4 mm , 2 mm and 14 mm , respectively , an average reduction of 11 2 mm after each treatment

In the case of a male aged 52 years (Case 9), who was suffering from tachycardia, observations of systolic pressure were made before and after the baths from the sixth to the seventeenth bath inclusive The results were as follows

Number of Bath	Systolic Pressure	
	Before	After
6	118	140
7	98	110
8	126	130
9	150	124
10	136	136
11	158	130
12	148	150
13	120	150
14	120	132
15	128	130
16	128	136
17	120	140

The systolic pressure was increased nine times, reduced twice and was unchanged once The increases of systolic pressure amounted to 22 mm , 12 mm , 4 mm , 2 mm , 30 mm , 12 mm , 2 mm , 8 mm and 20 mm , respectively, an average of 12 4 mm at each treatment The decreases of systolic pressure amounted to 26 mm and 28 mm , respectively , an average reduction of 27 mm at each treatment

In the case of a female aged 57 years (Case 30), who was suffering from fibroid myocarditis, observations of blood-pressure were made before and after each bath for five baths The blood-pressure observations made the patient excessively nervous and it was necessary to discontinue them after the fifth bath They were as follows

No of Bath	Before				After			
	Systolic	Diastolic	Mean	Pulse Pressure	Systolic	Diastolic	Mean	Pulse Pressure
1	180	130	155	50	210	170	190	40
2	170	150	160	20	184	132	158	52
3	180	118	149	62	214	152	183	62
4	186	132	159	54	164	120	142	44
5	202	150	176	52	176	118	147	58

The systolic pressure was raised three times and lowered twice. The elevations of systolic pressure were 30 mm, 14 mm and 34 mm, respectively, an average of 26 mm at each bath. The reductions in systolic pressure were 22 mm and 26 mm, respectively, an average of 24 mm and 10 mm, respectively, an average of 10 mm at each treatment.

The pulse-pressure was increased twice, reduced twice, and was unchanged once. The increases were 32 mm and 6 mm, respectively, an average of 19 mm at each treatment. The reductions were 10 mm and 10 mm respectively, an average of 10 mm at each treatment.

TABLE 3—MITRAL REGURGITATION WITH BEGINNING LOSS OF COMPENSATION  
BLOOD-PRESSURE OBSERVATIONS

No of Bath	B P Before Bath				B P After Bath			
	S	D	M	PP	S	D	M	PP
1	140	90	115	50	178	140	159	38
2	164	82	123	82	130	72	101	58
3	130	96	113	34	138	88	113	50
4	133	73	103	60	136	65	100.5	71
5	142	83	112.5	59	130	66	98	64
6	136	69	102.5	67	134	71	102.5	63
7	129	69	99	60	132	74	103	58
8	130	66	98	64	134	70	102	64
9*								
10	124	69	96.5	55	124	66	95	58
11	128	68	98	60	128	65	96.5	63
12*								
13	144	79	111.5	65	138	70	104	68
14	132	58	95	74	138	64	101	74
15*								
16*								
17	138	80	109	58	128	68	98	60
18	146	76	111	70	140	84	112	56

\*Observations missed

The study of these five cases, two of fibroid myocarditis, one of parenchymatous myocarditis, one of mitral regurgitation with beginning loss of compensation and one of tachycardia, shows that of sixty-six observations made immediately after the administration of the baths the systolic pressure was increased forty-three times, lowered eighteen times, and was unchanged five times. The pulse-pressure was increased twenty-eight times, lowered twenty-one times, and was unchanged five times out of the same number of observations. The highest elevation of systolic pressure recorded was 38 mm after the first bath in Case 3. The highest elevation of pulse-pressure recorded was 32 mm after the first bath in Case 30.

Thirty-four observations were made of systolic pressure and pulse-pressure one hour after the baths were given. The systolic pressure was higher than before the bath was given twenty times, lower twelve times, and was unchanged twice. The greatest increase was 19 mm after the eighteenth bath in Case 1.

The pulse-pressure was raised fourteen times, lowered sixteen times, and was unchanged four times. The highest elevation of pulse-pressure was 28 mm. after the eleventh bath in Case 1.

In these cases we probably get some idea of the effect of the treatment by baths on the blood-pressure. The majority of the observations, however, have had to be made by taking the blood-pressure at the beginning of the treatment and at its close. It must be borne in mind that nearly all of the patients were receiving other forms of treatment as well as carbonated brine baths. In Case 12 the patient received electric light baths alternating with the carbonated brine baths. Cases 8, 13, 38, 66 and 78 received carbonated brine baths on one day and resistance exercises on the alternate day. Case 15 had a carbonated brine bath one day and a Russian bath on the alternate day. Cases 74 and 75 (the same patient) had hot brine baths, massage and various forms of electricity. Cases 63, 64 and 65 (the same patient) had abdominal massage and colonic irrigations in addition to the carbonated brine baths.

All of the patients were in a restful environment, except for inherent restlessness and dissatisfaction on the part of some of them, all were on a carefully regulated diet, the components of which I have already published,<sup>4, 5</sup> and all were required to rest from one to two hours every day in addition to their time in bed at night, nine hours being prescribed.

#### ANALYSIS OF CASES

For purposes of analysis the cases may be divided in two ways: those patients who took the full course of treatment of six weeks, sixty; and those who for one reason or another did not complete the full number of baths, twenty-one; second, into the high-pressure cases and the low-pressure cases.

Table 4 gives the reading of the systolic pressure at the beginning and at the end of the treatment in those patients who received the full course of baths. The pressure was higher at the close of the course than at the beginning in thirty instances, lower in twenty-five instances and was unchanged in five instances. The greatest elevation of pressure was 50 mm. in a case of beginning interstitial nephritis, the greatest reduction 12 mm. in a case of fibroid myocarditis.

Table 5 gives the reading of the systolic pressure in those patients who took only partial courses. At the end of the baths the systolic pressure was found elevated nine times, lowered nine times and unchanged three times. The greatest elevation of pressure was 22 mm. in a case of tachycardia after twelve baths. The greatest reduction 29 mm. in a case of aortic regurgitation after ten baths.

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<sup>5</sup> Swan. *Inter-state Med Jour.*, June, 1911, xviii, 633.

Table 6 gives the effect on the diastolic pressure in the cases that received the full course of baths. The diastolic pressure was raised in twenty-six cases, lowered in twenty-eight cases, and no change was noted in six cases. The change in diastolic pressure did not always agree with the change in systolic pressure, when the systolic pressure was elevated the diastolic pressure may have been lowered, and vice versa. The greatest elevation of diastolic pressure was 36 mm. in a case of beginning interstitial nephritis, Case 7. The greatest lowering of diastolic pressure was 27 mm. in a case of fibroid myocarditis, Case 30.

Table 7 gives the details of the diastolic pressure in those patients who had only partial courses. The diastolic pressure was found elevated in eleven cases, lowered in eight cases and unchanged in two cases. The greatest elevation in pressure, 22 mm., was seen in a case of paroxysmal tachycardia, Case 64, after thirteen baths. The greatest lowering of diastolic pressure, 90 mm., was seen in a case of aortic regurgitation, after ten baths.

#### HIGH-PRESSURE CASES

As the result of the study of 1,000 cases of application for life insurance, Woley<sup>6</sup> has shown that the average blood-pressure of males at all ages is 127.5 mm., and of females 120 mm. His figures show an increase in the average blood-pressure in each decennial period so that in the sixth decennium the average high pressure is 149 mm., and the average systolic pressure of all applicants in the decennium is 132 mm.

Suppose then, disregarding the ages of the patients, we classify all the cases in this study that give a blood-pressure of over 150 mm. as high-pressure cases. Cases 2, 5, 6, 11, 13, 14, 15, 17, 18, 20, 30, 33, 35, 36, 38, 39, 41, 42, 43, 46, 50, 57, 59, 68, 69, 70, 73, 76 belong to this class.

Table 8 gives the details of the variations of pressure in these cases. It will be seen that the systolic pressure was raised in thirteen cases, lowered in thirteen cases, and was unchanged in two cases. The greatest elevation was 25 mm., in a case of dilatation of the heart (Case 20). The systolic pressure was raised from 186 mm. before the treatments were begun to 212 mm. at their conclusion.

The greatest lowering of systolic pressure was 42 mm., in a case of fibroid myocarditis (Case 35). In this case the systolic pressure was 184 mm. at the beginning of the course of treatment and 142 mm. at its close. The patient had an intermission of seven weeks in his treatment after his fifth bath. At that time his systolic pressure had been reduced from 184 mm. to 168 mm., 16 mm. On resuming his treatment the systolic pressure had further fallen to 150 mm., 18 mm., in spite of the fact that he had been attending to his business. If we exclude this case, the greatest lowering of systolic pressure was 40 mm. in a case of fibroid myocarditis (Case 42).

<sup>6</sup> Woley Jour. Am. Med. Assn., July 9, 1910, IV, 121

TABLE 4—SYSTOLIC BLOOD PRESSURES COMPLETE COURSES OF CARBONATED BRINE BATHS

No	Sex	Age	Systolic Pressure at		Difference, mm	Diagnosis
			Treatm't, mm	End of Treatm't, mm		
1	M	76	142	135	— 7	Fibroid Myocarditis
2	F	49	158	165	+ 7	Hypertrophy of the heart (Toxic)
3	F	20	140	145	+ 5	Mitral regurgitation
4	F	60	140	152	+12	Fibroid myocarditis
5	M	70	168	139	—29	Dilatation of the heart
6	F	69	150	162	+12	Fibroid myocarditis
7	M	45	124	174	+50	Beginning interstitial nephritis
8	F	37	116	124	+ 8	Hypertrophy and dilatation of the heart
10	F	56	145	140	— 5	Neurasthenia
11	M	36	155	157	+ 2	Hypertrophic cirrhosis of the liver
12	M	53	144	128	—16	Dilatation of the heart
13	F	70	170	170	0	Fibroid myocarditis
14	F	77	169	150	—19	Parenchymatous myocarditis
15	F	65	178	167	—11	Fibroid myocarditis, chronic bronchitis
16	F	26	115	118	+ 3	Parenchymatous myocarditis
17	M	67	152	161	+ 9	Chronic parenchymatous nephritis
18	M	68	207	190	—17	Mitral regurgitation
20	M	63	186	212	+26	Dilatation of heart
22	M	36	118	110	— 8	Mitral regurgitation, aortic regurgitation
23	M	67	144	140	— 4	Fibroid myocarditis
24	M	52	110	104	— 6	Mitral regurgitation
26	M	50	150	130	—20	Hypertrophy of the heart
27	M	45	109	117	+ 8	Parenchymatous myocarditis
28	M	62	135	140	+ 5	Dilatation of the heart
29	M	47	124	116	— 8	Dilatation of the heart
30	F	57	180	164	—16	Fibroid myocarditis
32	M	29	119	134	+15	Parenchymatous myocarditis
35	M	71	184	142	—42	Fibroid myocarditis (Baths in two installments)
40	M	35	112	102	—10	Parenchymatous myocarditis
42	F	54	154	114	—40	Fibroid myocarditis
43	F	49	162	142	—20	Hypertrophy and dilatation of the heart
44	M	23	120	120	0	Aortic regurgitation
45	F	35	120	132	+12	Convalescent from acute infection
46	F	60	178	200	+22	Fibroid myocarditis (same as No 4)
49	F	48	130	125	— 5	Fat heart
50	F	68	193	210	+17	Arteriosclerosis
51	M	69	140	135	— 5	Hypertrophy and dilatation of the heart
52	M	39	108	110	+ 2	Neurasthenia
53	M	54	107	109	+ 2	Hypochondriasis
54*	F	26	119	120	+ 1	Convalescent from appendectomy
55	F	33	90	95	+ 5	Gastrectasia
57	F	47	186	173	—13	Mitral regurgitation
58	M	27	126	125	— 1	Nervous dyspepsia
59	M	57	190	193	+ 3	Mitral regurgitation
60	M	39	119	128	+ 9	Parenchymatous myocarditis, infectious granuloma
62	M	60	126	112	—14	Parenchymatous myocarditis
63	M	54	150	150	0	Paroxysmal tachycardia
65	M	55	113	120	+ 7	Paroxysmal tachycardia (Same patient as No 63)
66	M	60	148	138	—10	Fibroid myocarditis
67	M	61	144	144	0	Mitral regurgitation (Same patient as No 66)

\*When the last observation was made on this patient she had just developed acute bronchitis

TABLE 4—SYSTOLIC BLOOD-PRESSURES COMPLETE COURSES OF CARBONATED BRINE BATHS  
(Continued)

Sex	Age	Systolic Pressure at		Difference mm	Diagnosis
		Begin of Treatm't mm	End of Treatm't, mm		
F	51	198	199	+ 1	Hypertrophy and dilatation of the heart
F	52	170	170	0	Hypertrophy and dilatation of the heart (Same patient as No 68 )
F	60	170	184	+14	Fibroid myocarditis
M	56	112	120	+ 8	Arthritis deformans with myocardial in sufficiency
M	56	118	125	+ 7	Same patient as No 74
M	71	162	168	+ 6	Dilatation of the heart (Same patient as No 5 )
F	70	140	138	— 2	Fibroid myocarditis
M	36	116	115	— 1	Dilatation of the heart (Same patient as No 25 )
F	54	118	122	+ 4	Dilatation of the heart (Same patient as No 37 )
F	49	130	156	+26	Hypertrophy of the heart (Same patient as No 2 after operation )

TABLE 5—SYSTOLIC BLOOD-PRESSURE, INCOMPLETE CARBONATED BRINE COURSES

Sex	Age	Systolic Pressure at		Differ- ence, mm	No of Baths	Diagnosis
		Begin of Treatm't, mm	End of Treatm't, mm			
M	52	118	140	+22	12	Tachycardia
M	57	134	134	0	6	Dilatation of heart
M	53	100	100	0	11	Fibroid myocarditis      Subacute bronchitis
M	35	130	116	—14	9	Dilatation of heart
F	65	125	119	— 6	9	Weak heart muscle
M	52	188	168	—20	3	Aortic regurgitation
M	58	120	120	0	11	Fibroid myocarditis
M	72	188	199	+11	9	Fibroid myocarditis
F	53	124	115	— 9	11	Beginning arteriosclerosis
F	70	162	140	—22	11	Diabetes mellitus
F	45	185	180	— 5	9	Convalescent from operation
M	58	156	166	+10	11	Hypertrophy of the heart
F	19	109	118	+ 9	11	Convalescent from typhoid fever
M	62	105	120	+15	11	Parenchymatous myocarditis
M	38	108	120	+12	9	Parenchymatous myocarditis
M	77	149	135	—14	12	Hypertrophy of the heart
M	54	125	136	+11	13	Paroxysmal tachycardia (same pa- tient as No 63)
M	30	174	145	—29	10	Aortic regurgitation
M	35	115	125	+10	8	Pulmonary emphysema
M	48	110	115	+ 5	7	Convalescent from influenza
M	52	137	130	— 7	5	Dilatation of the heart



TABLE 6—DIASTOLIC BLOOD PRESSURE COMPLETE CARBONATED BRINE COURSES

No	Sex	Age	Diastolic Pressure at Begin of Treatment, End of Treatment, Difference,		
			mm	mm	mm
1	M	76	85	80	— 5
2	F	49	108	104	— 4
3	F	20	90	80	—10
4	F	60	86	70	—16
5	M	70	96	80	—16
6	F	69	84	79	— 5
7	M	45	90	126	+36
8	F	37	74	74	0
10	F	56	70	75	+ 5
11	M	36	92	90	— 2
12	M	53	80	75	— 5
13	F	70	112	105	— 7
14	F	77	94	76	—18
15	F	65	92	100	+ 8
16	F	26	60	63	+ 3
17	M	67	93	80	—13
18	M	68	110	100	—10
20	M	63	100	108	+ 8
22	M	36	75	95	+20
23	M	67	80	85	+ 5
24	M	52	72	68	— 4
26	M	50	90	83	— 7
27	M	45	66	69	+ 3
28	M	62	92	103	+11
29	M	47	83	72	—11
30	F	57	130	103	—27
32	F	29	75	82	+ 7
35	M	71	118	88	—30
40	M	35	70	70	0
42	F	54	112	76	—46
43	F	49	112	86	—36
44	M	23	50	36	—14
45	F	35	82	72	—10
46	F	60	90	80	—10
49	F	48	78	90	+12
50	F	68	85	79	— 6
51	M	69	75	75	0
52	M	39	62	76	+14
53	M	54	60	78	+18
54	F	26	67	80	+13*
55	F	33	55	75	+20
57	F	47	103	105	+ 2
58	M	27	70	80	+10
59	M	57	119	125	+ 6
60	M	39	78	78	0
62	M	60	98	75	—23
63	M	54	93	90	— 3
65	M	55	70	70	0
66	M	60	76	76	0
67	M	61	62	68	+ 6
68	F	51	100	90	—10
69	F	52	85	95	+10
73	F	60	85	87	+ 2
74	M	56	77	78	+ 1
75	M	56	102	80	—22
76	M	71	84	90	+ 6
77	F	70	70	72	+ 2
78	M	56	73	75	+ 2
80	F	54	70	68	— 2
81	F	49	95	125	+30

\*When the last observation was made on this patient she had just developed nephritis.

TABLE 7 — DIASTOLIC BLOOD-PRESSURES INCOMPLETE CARBONATED BRINE COURSES

No	Sex	Age	Diastolic Pressure at		Difference, mm	No of Baths
			Treatment, mm	End of Treatment, mm		
9	M	52	80	100	+20	12
19	M	57	96	100	+ 4	6
21	M	53	62	64	+ 2	11
25	M	35	78	80	+ 2	9
31	F	65	81	70	—11	9
33	M	52	78	70	— 8	3
34	M	58	84	84	0	11
36	M	72	100	96	— 4	9
37	F	53	70	71	+ 1	11
38	F	70	76	72	— 4	11
39	F	45	95	95	0	9
41	M	58	104	110	+ 6	11
47	F	19	58	64	+ 6	11
48	M	62	65	66	+ 1	11
56	M	38	65	74	+ 9	9
61	M	77	88	83	— 5	12
64	M	54	82	104	+22	13
70	M	30	90	0	—90	10
71	M	35	80	78	— 2	8
72	M	48	72	65	— 7	7
79	M	52	85	86	+ 1	5

TABLE 8 — HIGH PRESSURE CASES SYSTOLIC PRESSURE ABOVE 150 MM

Case No	Variation of Pressure			Pulse	Number of Baths
	Systolic	Diastolic	Mean		
2	+ 7	— 4	+ 1 5	+11	18
5	—29	—16	—22 5	—13	18
6	+12	— 5	+ 3 5	+16	18
11	+ 2	— 2	0	+ 4	18
13	0	— 7	— 3 5	+ 7	18
14	—19	—18	—18 5	— 1	18
15	—11	+ 8	— 1 5	—19	18
17	+ 9	—13	— 2	+22	18
18	—17	—10	—13 5	— 7	18
20	+26	+ 8	+17	+18	18
30	—16	—27	—21 5	+11	18
33	—20	— 8	—14	—12	3
35	—42	—30	—36	—12	18
36	+11	— 4	+ 3 5	+15	9
38	—22	— 4	—13	—18	11
39	— 5	0	— 2 5	— 5	9
41	+10	+ 6	+ 8	+ 4	11
42	—40	—46	—43	+ 6	18
43	—20	—36	—23	+ 6	18
46	+22	—10	+ 6	+32	18
50	+17	— 6	+ 5 5	+23	18
57	—13	+ 2	— 5 5	—15	18
59	+ 3	+ 6	+ 4 5	— 3	18
68	+ 1	—10	— 4 5	+11	18
69	0	+10	+ 5	—10	18
70	—29	—90	—59 5	+61	10
73	+14	+ 2	+ 8	+12	18
76	+ 6	+ 6	+ 6	0	18

TABLE 9—LOW PRESSURE CASES    SYSTOLIC PRESSURE 150 MM, OR BELOW

Case No	Variation of Pressure			Pulse	Number of Baths
	Systolic	Diastolic	Mean		
1	— 7	— 5	— 6	— 2	18
3	+ 5	—10	— 3.5	+15	18
4	+12	—16	— 2	+28	18
7	+50	+36	+43	+14	18
8	+ 8	0	+ 4	+ 8	18
9	+22	+20	+21	+ 2	12
10	— 5	+ 5	0	—10	18
12	—16	— 5	—10.5	— 9	18
16	+ 3	+ 3	+ 3	0	18
19	0	+ 4	+ 2	— 4	6
21	0	+ 2	+ 1	— 2	11
22	— 8	+20	+ 6	—28	18
23	— 4	+ 5	+ 0.5	— 9	18
24	— 6	— 4	— 5	— 2	18
25	—14	+ 2	— 6	—16	9
26	—20	— 7	—13.5	—13	18
27	+ 8	+ 3	+ 5.5	— 5	18
28	+ 5	+11	+ 8	— 6	18
29	— 8	—11	— 9.5	— 3	18
31	— 6	—11	— 8.5	+ 5	9
32	+15	+ 7	+11	+ 8	18
34	0	0	0	0	11
37	— 9	+ 1	— 4	—10	11
40	—10	0	— 5	—10	18
44	0	—14	— 7	+14	18
45	+12	—10	+ 1	+12	18
47	+ 9	+ 6	+ 7.5	+ 3	11
48	+15	+ 1	+ 8	+14	11
49	— 5	+12	+ 3.5	—17	18
51	— 5	0	— 2.5	— 5	18
52	+ 2	+14	+ 8	—12	18
53	+ 2	+18	+10	—16	18
54	+ 1	+13	+ 7	—12	18
55	+ 5	+20	+12.5	—15	18
56	+12	+ 9	+10.5	+ 3	9
58	— 1	+10	+ 4.5	—11	18
60	+ 9	0	+ 4.5	+ 9	18
61	—14	— 5	— 9.5	— 9	12
62	—14	—23	—18.5	+ 9	18
63	0	— 3	— 1.5	+ 3	18
64	+11	+22	+16.5	—11	13
65	+ 7	0	+ 3.5	+ 7	18
66	—10	0	— 5	—10	18
67	0	+ 6	+ 3	— 6	18
71	+10	— 2	+ 4	+22	8
72	+ 5	— 7	— 1	+12	7
74	+ 8	+ 3	+ 5.5	+ 5	18
75	+ 7	—22	— 7.5	+29	18
77	— 2	+ 2	0	— 4	18
78	— 1	+ 2	+ 0.5	— 3	18
79	— 7	+ 1	— 3	— 8	5
80	+ 4	— 2	+ 1	+ 6	18
81	+26	+30	+28	— 4	18

The diastolic pressure was raised in eight cases, lowered in nine cases, and was unchanged in one case. The greatest elevation was 8 mm in two cases, one of fibroid myocarditis with chronic bronchitis (Case 1) and one of dilatation of the heart (Case 20). In the former the diastolic pressure was 92 mm at the beginning of the treatments and 100 mm at the end; in the latter the diastolic pressure rose from 100 mm, at beginning of the treatments, to 108 mm at their close.

The greatest reduction of diastolic pressure was 90 mm, in a case of aortic regurgitation (Case 70) after ten treatments. In a case of hypertrophy and dilatation of the heart (Case 43) the diastolic pressure was reduced 36 mm, from 112 mm at the beginning of the treatments to 76 mm at their close. In a case of myocarditis (Case 42) the diastolic pressure was reduced 46 mm, from 112 mm at the beginning of the treatments to 66 mm at the end.

The mean pressure in these cases was raised eleven times, lowered sixteen times and was unchanged once. The greatest elevation of the mean pressure was 17 mm, in a case of dilatation of the heart (Case 20). The greatest reduction of mean pressure was 59.5 mm, in a case of aortic regurgitation (Case 70).

The pulse-pressure in these cases was raised sixteen times, reduced eleven times and was unchanged once. The greatest elevation of pulse-pressure was 61 mm, in a case of aortic regurgitation (Case 70). The greatest reduction in pulse-pressure was 19 mm, in a case of fibroid myocarditis with chronic bronchitis (Case 15).

Case 70 was a case of aortic regurgitation in a young man, aged 25 years. On admission he had dilatation of the heart as well as hypertrophy and the murmur of mitral regurgitation, as well as a double aortic murmur. The aortic diastolic murmur, however, was not loud and was not well transmitted. His blood-pressure showed a well-marked fifth phase at 90 mm, giving him a pulse-pressure of 84 mm.

After ten carbonated bismuth baths, which were given in groups of three baths with an interval of one day between each group of baths, the transverse diameter of his cardiac dulness was found to be  $3\frac{3}{4}$  inch instead of  $5\frac{3}{4}$  inches which was the record on admission. The point of maximum intensity of the cardiac impulse had moved in from 5 inches to the left of the midsternal line in the sixth interspace, to the midclavicular line in the sixth interspace. The murmur of mitral regurgitation, although still present, was not as loud as it had been at admission and was not transmitted to the angle of the scapula. The murmur of aortic regurgitation was still present. The pulse was more positively of the Corrigan type. The blood-pressure observations gave a systolic reading of 145 mm, but there were no phases. The tap could be heard with no pressure in the cuff. Consequently, the diastolic pressure could be considered 0, the mean pressure 72.5 and the pulse-pressure 145.

Gitting,<sup>7</sup> and Goodman and Howell<sup>8,9</sup> have pointed out the absence of phases and a diastolic pressure of 0 in cases of aortic regurgitation

#### LOW-PRESSURE CASES

Cases 1, 3, 4, 7, 8, 9, 10, 12, 16, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 31, 32, 34, 37, 40, 44, 45, 47, 48, 49, 51, 52, 53, 54, 55, 56, 58, 60, 61, 62, 63, 64, 65, 66, 67, 71, 72, 74, 75, 77, 78, 79, 80 and 81 may be looked on as low-pressure cases (Table 9) In these the systolic pressure was raised in twenty-six cases, reduced in twenty-one cases and was unchanged in six cases The greatest increase in systolic pressure was 50 mm, in a case of beginning interstitial nephritis (Case 7) The patient had a systolic pressure of 124 mm at the beginning of the treatments, and at the end of the course his systolic pressure had increased to 174 mm

The greatest reduction of systolic pressure was 20 mm, in a case of hypertrophy of the heart (Case 26) The systolic pressure was 150 mm at the beginning of the treatments, and 130 mm at the end

The diastolic pressure was increased in twenty-nine cases, reduced in seventeen cases and was unchanged in seven cases The greatest elevation of diastolic pressure was 36 mm, in a case of beginning interstitial nephritis (Case 7). The patient had a diastolic pressure of 90 mm at the beginning of the treatments, and 126 mm at their close The greatest reduction of diastolic pressure was 23 mm, in a case of parenchymatous myocarditis (Case 62) At the beginning of the treatments the diastolic pressure was 98 mm, and at their close it was 75 mm This patient was 60 years of age

The mean pressure was elevated in thirty cases, reduced in twenty cases and was unchanged in three cases The greatest increase in mean pressure was 43 mm, in a case of beginning interstitial nephritis (Case 7) The greatest decrease in mean pressure was 18.5 mm, in a case of parenchymatous myocarditis (Case 62)

The pulse-pressure was elevated in twenty-three cases, reduced in thirty cases and was unchanged in two cases The greatest elevation of pulse-pressure was 29 mm, in a case of arthritis deformans with myocardial insufficiency (Case 75) The greatest reduction in pulse-pressure was 28 mm in a case of mitral regurgitation and aortic regurgitation (Case 22)

#### FIBROID MYOCARDITIS

Cases 1, 4, 6, 13, 15, 21, 23, 30, 34, 35, 36, 42, 46, 66, 73 and 77 are cases of fibroid myocarditis (Table 10)

7 Gittings THE ARCHIVES INT MED, August, 1910, vi, 196

8 Goodman and Howell Univ Penn Med Bull, November, 1910, xiii, 469

9 Goodman and Howell Am Jour Med Sc, September, 1911, cxlii, 334

In these cases the systolic pressure was raised in five, reduced in eight and no change was noted in three. The greatest elevation of systolic pressure was 22 mm, in Case 46, the greatest reduction was 42 mm, in Case 35.

The diastolic pressure was raised in five cases, reduced in nine cases and was unchanged in two cases. The greatest elevation was 8 mm, in Case 15; the greatest reduction 30 mm, in Case 35.

The mean pressure was raised in six cases, lowered in eight cases, and was unchanged in two cases. The greatest elevation of mean pressure was 8 mm, in Case 73, the greatest reduction was 43 mm, in Case 42.

The pulse-pressure was increased in eight cases, reduced in seven cases and was unchanged in one case. The greatest elevation of pulse-pressure was 32 mm, in Case 46, the greatest reduction was 19 mm, in Case 15.

TABLE 10—CASES OF FIBROID MYOCARDITIS

Case No	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
1	— 7	— 5	— 6	— 2	18
4	+12	—16	— 2	+28	18
6	+12	— 5	+ 3.5	+16	18
13	0	— 7	— 3.5	+ 7	18
15	—11	+ 8	— 1.5	—19	18
21	0	+ 2	+ 1	— 2	11
23	— 4	+ 5	+ 0.5	— 9	18
30	—16	—27	—21.5	+11	18
34	0	0	0	0	11
35	—42	—30	—36	—12	18
36	+11	— 4	+ 3.5	+15	9
42	—40	—46	—43	+ 6	18
46	+22	—10	+ 6	+32	18
66	—10	0	— 5	—10	18
73	+14	+ 2	+ 8	+12	18
77	— 2	+ 2	0	— 4	18

#### PARENCHYMATOUS MYOCARDITIS

Cases 14, 16, 27, 32, 40, 48, 56, 60 and 62 are cases of parenchymatous myocarditis (Table 11).

The systolic pressure was raised in six of these cases and was reduced in three. The greatest elevation of systolic pressure was 15 mm, in Cases 32 and 48, the greatest reduction was 19 mm, in Case 14.

The diastolic pressure was raised in five cases, lowered in two cases, and was unchanged in two cases. The greatest elevation was 9 mm, in Case 56, the greatest reduction was 23 mm, in Case 62.

The mean pressure was raised in six cases and lowered in three cases. The greatest elevation was 11 mm, in Case 32, the greatest reduction was 18.5 mm, in Cases 14 and 62.

The pulse-pressure was increased in five cases, reduced in three cases and was unchanged in one case. The greatest elevation of pulse-pressure was 14 mm, in Case 48, the greatest reduction was 10 mm, in Case 40.

TABLE 11—CASES OF PARENCHYMATOUS MYOCARDITIS

Case No	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
14	—19	—18	—18.5	—1	18
16	+3	+3	+3	0	18
27	+8	+3	+5.5	—5	18
32	+15	+7	+11	+8	18
40	—10	0	—5	—10	18
60	+9	0	+4.5	+9	18
62	—14	—23	—18.5	+9	18
48	+15	+1	+8	+14	11
56	+12	+9	+10.5	+3	9

## DILATATION OF THE HEART

Cases 5, 12, 19, 20, 25, 28, 29, 76, 78, 79 and 80 are cases of dilatation of the heart (Table 12)

In four of these cases the systolic pressure was raised, in six it was lowered and in one no change was noted. The greatest elevation of systolic pressure was 26 mm, in Case 20, the greatest depression was 29 mm, in Case 5

The diastolic pressure was raised in seven cases and lowered in four. The greatest elevation of diastolic pressure was 11 mm, in Case 28, the greatest reduction was 16 mm, in Case 5

The mean pressure was raised in six cases and lowered in five cases. The greatest elevation was 17 mm, in Case 20, the greatest reduction was 22.5 mm, in Case 5

The pulse-pressure was raised in two cases, lowered in eight cases and no change was noted in one case. The greatest increase in pulse-pressure was 18 mm, in Case 20, the greatest decrease was 16 mm, in Case 25

TABLE 12—CASES OF DILATATION OF THE HEART

Case No	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
5	—29	—16	—22.5	—13	18
12	—16	—5	—10.5	—9	18
19	0	+4	+2	—4	6
20	+26	+8	+17	+18	18
25	—14	+2	—6	—16	9
28	+5	+11	+8	—6	18
29	—8	—11	—9.5	—3	18
76	+6	+6	+6	0	18
78	—1	+2	+0.5	—3	18
79	—7	+1	—3	—8	5
80	+4	—2	+1	+6	18

## HYPERTROPHY AND DILATATION OF THE HEART

Cases 8, 43, 51, 68 and 69 are cases of hypertrophy and dilatation of the heart (Table 13)

The systolic pressure in these cases was raised twice, lowered twice and no change was observed once. The greatest increase in systolic pressure was 8 mm, in Case 8, the greatest decrease of systolic pressure was 20 mm in Case 43

The diastolic pressure was raised once, lowered twice and no change was noted twice. The elevation amounted to 10 mm, in Case 69. The greatest reduction of diastolic pressure was 36 mm, in Case 43.

The mean pressure was raised twice and lowered three times. The greatest elevation of mean pressure was 5 mm, in Case 69, the greatest reduction was 23 mm, in Case 43.

The pulse-pressure was raised three times and lowered twice. The greatest elevation of pulse pressure was 11 mm, in Case 68, the greatest decrease in pulse-pressure was 10 mm, in Case 69.

TABLE 13—CASES OF HYPERTROPHY AND DILATATION OF THE HEART

Case No	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
8	+ 8	0	+ 4	+ 8	18
43	-20	-36	-23	+ 6	18
51	- 5	0	- 2.5	- 5	18
68	+ 1	-10	- 4.5	+11	18
69	0	+10	+ 5	-10	18

## MITRAL REGURGITATION

Cases 18, 24, 57, 59 and 67 are cases of mitral regurgitation (Table 14). In these cases the systolic pressure was raised once, reduced three times and no change was observed once. The increase of systolic pressure amounted to 3 mm, in Case 59. The greatest reduction of systolic pressure amounted to 17 mm, in case 63.

The diastolic pressure was raised in three cases and was reduced in two cases. The greatest increase of diastolic pressure was 6 mm, in Cases 59 and 67. The greatest reduction of diastolic pressure was 10 mm, in Case 18.

The mean pressure was raised twice and lowered three times. The greatest increase of mean pressure was 4.5 mm, in Case 59. The greatest decrease of mean pressure was 13.5 mm, in Case 18.

The pulse-pressure was reduced in every case, the greatest reduction was 15 mm, in Case 57.

TABLE 14—CASES OF MITRAL REGURGITATION

Case No	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
18	-17	-10	-13.5	- 7	18
24	- 6	- 4	- 5	- 2	18
57	-13	+ 2	- 5.5	-15	18
59	+ 3	+ 6	+ 4.5	- 3	18
67	0	+ 6	+ 3	- 6	18

## HYPERTROPHY OF THE HEART

Cases 2, 26, 41, 61 and 81 are cases of hypertrophy of the heart (Table 15). In these cases the systolic pressure was increased in three and reduced in two. The greatest increase of systolic pressure was 26 mm, in Case 81. The greatest reduction in systolic pressure was 20 mm, in Case 26.



The diastolic pressure was increased in two cases and reduced in three cases. The greatest increase of diastolic pressure was 30 mm, in Case 81, the greatest reduction of diastolic pressure was 7 mm, in Case 26.

The mean pressure was increased in three cases and reduced in two. The greatest increase in mean pressure was 28 mm, in Case 81 and the greatest reduction in mean pressure was 13.5 mm, in Case 26.

The pulse-pressure was increased in two cases and reduced in three cases. The greatest increase in pulse-pressure was 11 mm, in Case 2, the greatest reduction in pulse-pressure was 13 mm, in Case 26.

TABLE 15—CASES OF HYPERTROPHY OF THE HEART

Case No	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
2	+ 7	— 4	+ 1.5	+11	18
26	—20	— 7	—13.5	—13	18
41	+10	+ 6	+ 8	+ 4	11
61	—14	— 5	— 9.5	— 9	12
81	+26	+30	+28	— 4	18

## TACHYCARDIA

Cases 9, 63, 64 and 65 are cases of tachycardia (Table 16). The systolic pressure was increased in three of these cases and no change was noted in the other one. The greatest increase of systolic pressure was 22 mm, in Case 9.

The diastolic pressure was increased in two of the cases, diminished in one, and no change was noted in the other one. The greatest increase of diastolic pressure was 22 mm, in Case 64. The reduction of diastolic pressure was 3 mm, in Case 63.

The mean pressure was raised in three of the cases and lowered in one. The greatest elevation of mean pressure was 21 mm, in Case 9. The reduction of mean pressure was 1.5 mm in Case 63.

The pulse-pressure was increased in three of the cases and reduced in the other one. The greatest increase of pulse-pressure was 7 mm, in Case 65, the reduction of pulse pressure was 11 mm in Case 64.

TABLE 16—CASES OF TACHYCARDIA

Case No	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
9	+22	+20	+21	+ 2	12
63	0	— 3	— 1.5	+ 3	18
64	+11	+22	+16.5	—11	13
65	+ 7	0	+ 3.5	+ 7	18

## AORTIC REGURGITATION

Cases 33, 44 and 70 are cases of aortic regurgitation (Table 17). The systolic pressure was diminished in two of these cases and no change was noted in the other one. The greatest reduction of pressure was 29 mm in Case 70.

The diastolic pressure was reduced in all three cases. The greatest reduction was 90 mm in Case 70.

The mean pressure was reduced in all three of the cases. The greatest reduction was 59.5 mm, in Case 70.

The pulse pressure was increased in two of the cases and diminished in the third. The greatest increase of pulse-pressure was 61 mm, in Case 70, the diminution of pulse-pressure amounted to 12 mm, in Case 33.

TABLE 17—CASES OF AORTIC REGURGITATION

Case No	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
33	—20	—8	—14	—12	3
44	0	—14	—7	+14	18
70	—20	—90	—59.5	+61	10

## ARTERIOSCLEROSIS

Cases 37 and 50 are cases of arteriosclerosis (Table 18). In one of these cases the systolic pressure was increased and in the other one it was diminished. The diastolic pressure, the mean pressure and the pulse-pressure were increased in one case and diminished in the other.

TABLE 18—CASES OF ARTERIOSCLEROSIS

Case No	Variation of Pressure				Number of Baths
	Systolic	Diastolic	Mean	Pulse	
37	—9	+1	—4	—10	11
50	+17	—6	+5.5	+23	18

In the case of mitral obstruction and regurgitation (Case 3), the systolic pressure was increased, the diastolic pressure and the mean pressure were reduced, and the pulse-pressure was increased.

In the case of chronic parenchymatous nephritis (Case 17), the systolic pressure was increased, the diastolic and mean pressure were reduced, and the pulse-pressure was increased.

In the case of beginning interstitial nephritis (Case 7), the systolic pressure was increased 50 mm, the diastolic pressure was increased 36 mm, the mean pressure was increased 43 mm, and the pulse-pressure was increased 14 mm.

In the case of mitral regurgitation and aortic regurgitation (Case 22), the systolic pressure was reduced, the diastolic and mean pressure were increased and the pulse-pressure was reduced.

In the case of fat heart (Case 49), the systolic pressure was reduced, the diastolic pressure and the mean pressure were increased and the pulse-pressure was reduced.

In the case of weak heart (Case 30), the systolic pressure, the diastolic pressure and the mean pressure were reduced but the pulse-pressure was increased.

## CONCLUSIONS

1 Carbonated brine baths have no constant effect on the blood-pressure of the human subject.

2 In the cases in which observations were made both before and after each bath the systolic pressure was raised more frequently than it

was lowered, so that we may say that the tendency of the baths is to raise the blood-pressure

3 Although there are cases of high blood-pressure in which a course of carbonated brine baths has been followed by a lower systolic pressure, there are other cases of high-pressure in which the pressure has been higher at the end of the course of treatment than it was at the beginning, in one case 26 mm higher

4 Although there are cases of low blood-pressure in which a course of carbonated brine baths has been followed by a higher systolic pressure, there are other cases of low pressure in which the pressure has been lower at the end of the course of treatment than it was at the beginning, in one case 20 mm lower

5 There is no method of determining in advance whether a given treatment will be followed by an elevation or by a fall of pressure

6 In the eighty-one cases the systolic pressure was higher at the end of the course of treatment than at the beginning in thirty-nine, lower in thirty-four, and unchanged in eight

7 In cases of fibroid myocarditis the pressure effect is inconstant In this series of cases the systolic pressure was lowered more often than it was raised, but the pulse-pressure was raised more often than it was lowered It seems to me a dangerous procedure to use a form of treatment in a case of cardiac fibrosis which may be followed by an increase of systolic pressure of 22 mm, or an increase of pulse-pressure of 32 mm

8 In cases of parenchymatous myocarditis the effect of the baths on blood-pressure is usually to raise it, but in some cases the baths are followed by a reduction of both the systolic and the pulse-pressures

9 In cases of dilatation of the heart, cases of hypertrophy and dilatation of the heart, cases of mitral regurgitation, cases of hypertrophy of the heart, cases of tachycardia, and cases of aortic regurgitation, the same uncertainty of results was seen, except that in cases of mitral regurgitation the pulse-pressure was reduced in every one of the five cases and in cases of aortic regurgitation the diastolic pressure and the mean pressure were reduced in every one of three cases

10 In a case of arteriosclerosis an increase of 17 mm in the systolic pressure and 23 mm in pulse-pressure might result disastrously In a case of chronic parenchymatous nephritis an increase of 9 mm in systolic pressure and of 22 mm in pulse-pressure may or may not be negligible In a case of interstitial nephritis an increase of 50 mm in systolic pressure could hardly be thought desirable

11 The reduction of systolic pressure in a case of weak heart can scarcely be looked on as a favorable circumstance

12 The benefit in the subjective symptoms in cases of heart disease which follows a course of carbonated brine baths is not dependent on the influence of the treatment on the blood-pressure

# A CLINICAL STUDY OF THE EFFECTS OF SLEEP AND REST ON BLOOD-PRESSURE \*

HARLOW BROOKS, M D

AND

JOHN H CARROLL, M D

NEW YORK

Numerous physiological researches on both man and the lower animals have shown that there is a marked fall in blood-pressure during sleep. Tarchanoff<sup>1</sup> showed that a fall in aortic pressure of from 20 to 50 mm mercury took place in young dogs during the early stages of sleep, and Howell<sup>2</sup> noted a like fall in the blood-pressure of man.

Leonard Hill,<sup>3</sup> although admitting that a fall in pressure took place, did not believe that this drop was any greater during sleep than that which has been demonstrated to occur as a result of simple rest combined with the prone posture. Brush and Fayerweather,<sup>4</sup> however, showed definitely that this was not the case, but that the fall was concurrent with sleep, and that it was much greater than the drop which sometimes, but not invariably, takes place simply from rest or on lying down.

Howell (Textbook) brings out the important fact that the maximum fall occurs between one and two hours after sleep, and that this same period corresponds to the time of the greatest auditory insensibility, as determined by Kohlschutter, Czerny, and by Moirghenthal and Priesbergen.

Our attention was first called to these physiological facts in the course of the study of a case of a peculiar mental and spinal phenomena, manifested in an instance of disturbed cerebrospinal circulation. Further investigation conducted on carefully selected cases showed that in each individual a more or less constant variation in the blood-pressure occurred, depending apparently more on the time of observation than on other factors. For example, we found that the night pressures, taken in groups of night sleepers, were almost invariably lower than the day pressures in the same individuals, but that conversely in night workers (ten instances studied) and day sleepers the finding was reversed. In the

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\* Read at the meeting of the Association of American Physicians, May 14, 1912

† From the Second Medical Service, City Hospital

‡ Manuscript submitted for publication, May 22, 1912

1 Tarchanoff Arch Ital de Biol 1894 vii, 318

2 Howell Jour Exp Med, 1897, ii, 335

3 Hill Lancet, London 1898 i, 282

4 Brush and Fayerweather Am Jour Physiol 1901 v 199

hope that a careful study of these conditions might lead to an understanding of the subject which might be utilized clinically, we then undertook a quite extensive study of the subject, after we had first verified on patients the correctness as applied to them, of the general physiological facts above cited

All of our observations were made using the 12 cm stiff leather arm cuff, and in most instances either the Janeway or the Sahlh sphygmomanometers were employed. For obvious reasons the study was confined to the systolic pressure. In most instances observations on individuals or groups of cases were corrected or verified by subsequent repetition under as nearly as possible the same conditions. In so far as practical, neurotic individuals and such others as through personal peculiarities, would be likely to confuse or complicate the main points of our study were avoided or eventually excluded from the statistical study, and an effort was made to select such instances as would appear to apply most fittingly to the question immediately under discussion, although these aberrant cases afforded a rich material of great interest. Naturally it was found that phlegmatic subjects showed much less hourly variations, such as might be excited by psychic stimulation, for this reason neurotic subjects were avoided in so far as possible, or their records were discarded when the data were considered statistically.

For convenience of study and purely from the clinical standpoint, we have divided our series of carefully observed cases into three classes. Those in which the systolic pressure lay within the range of the usual, 110 to below 170 mm Hg, those in which the pressure was less than the usual, that is below 110 mm, and those in which the pressure was above 170 mm Hg, which class comprised the high-pressure cases. In order that widely discordant results might not be reached from this division into more or less arbitrary classes, excessive alterations in pressure were not included in our tabulated series, though special but entirely individual studies have been made in many such instances. Thus, for example, the very low systolic pressure of 65 mm in a case of salvarsan poisoning was not included, nor were two instances of systolic pressure of 300 and 310 mm, respectively included.

In each series a basis of comparison was established by taking the pressure in each case between 4 and 5 p. m., for as we have shown, the time of the day, at least in its relation to rhythmic sleep, is an important matter when one comes to comparatively estimate and particularly to value blood-pressure. Each group was investigated and recorded not less than four times, and most cases were kept on regular pressure charts throughout.

Sixty-eight patients who showed medium pressures were studied. These gave an average basic afternoon pressure of 142.5 mm. Systolic

readings taken between one and two hours after the night sleep showed an average drop of 24 mm Hg. Three hours after the morning waking the pressure still showed an average depression of 12 mm, and from this time during the day the pressure gradually rose until the mean afternoon level was again reached, between 4 and 5 o'clock.

Thirty instances of low pressure were similarly studied. The group showed an average systolic pressure of 100 mm (the minimum case had a pressure of 80 mm). Pressure determined within from one to two hours after primary sleep showed an average drop of 16.5 mm. The morning reading still showed an average depression of 6.66 mm with a slow return to the general average of evening pressure.

Twenty-nine cases of high-pressure with an average systolic reading of 204.5 and a maximum in two cases of 250 mm, showed an average one- to two-hour drop of 44.8 mm and a morning pressure of 22.8.

It is a noteworthy fact that the least drop in pressure took place in those patients who had an initial low-pressure and the greatest fall in those with the highest systolic reading. Study of isolated examples of very high and of very low pressure show this fact in even more marked degree. Just as under physiological conditions the maximum fall occurs within two hours after falling asleep, with a subsequent slow rise culminating in the afternoon reading.

That this fall is a definite attempt at conservation on the part of nature, needs no very vivid imagination to conceive.

Observations conducted on these and other groups of selected cases, including also neurotic subjects, indicate that the preliminary drop after sleep is a very rapid one and that the rise thereafter begins during sleep, very soon after the point of minimum pressure and extends up gradually through the remainder of the sleep period, to slowly rise during the day until the maximum pressure of the afternoon is reached. This is the course when patients are confined to bed, but when they are allowed to rise and go about the ward there is a slight but rapid rise of a few mm incident to getting up, after which the usual slow upward curve ensues, and except in this particular no essential difference between bed and ambulatory cases is demonstrable.

Although it might reasonably be inferred from the foregoing that a regular blood-pressure curve exists not only in normal but also in super- and subnormal cases, and while such is true of the average case, many exceptions exist, especially in subjects markedly influenced by various psychic factors and particularly as we have demonstrated to our own satisfaction in cases of circulatory decompensation or in cases about to decompensate.

The marked effect of nervousness and apprehension in influencing the blood-pressure curve has not, we believe, been overestimated by

clinicians, and as before mentioned, in our systematic groups we have attempted insofar as practical, to eliminate those patients in whom this factor was likely to be a dominant one

Gumprecht found a fall in the pressure of laboring men with readings between 160 and 200 mm, after rest in bed on their entrance into the hospital, and he attributes this drop to unaccustomed rest Hensen,<sup>5</sup> however, calls attention to the higher readings usual in patients of this class on the first day of their hospital residence We are inclined from our studies to agree with Hensen, for we have not found that rest *per se*, that is, physical rest, materially alters either super- or normal blood-pressure, although it exerts a profound elevating influence on the low pressures of exhaustion Concerning mental or psychic rest or sedation, however, we are strongly of the opinion that profound changes in pressure occur, and although we have not as yet proved it to our complete satisfaction, we believe that these factors determine to a very large degree the undoubted benefit derived from rest in cases of high pressure

It is admittedly foreign to the nature and intent of this paper to enter into an attempt at physiological interpretation of the fall of blood-pressure after sleep, but the subject is so alluring and admits of so very many interesting and possibly therapeutically important inferences that it is difficult totally to abstain in this direction From a somewhat limited number of observations conducted alike on high, medium and low pressure cases, it seems that the fall in pressure after sleep is much more pronounced after the customary regular or rhythmic sleep, be this night or day, while the drop which also occurs as a result of the sleep taken at irregular intervals is usually much less in degree and less abrupt in appearance, although we have some evidence to the effect that after profound physical exhaustion the drop in pressure which occurs with sleep is even more rapid, but it does not fall much if any below the accustomed level which we believe from these clinical cases to be an *individual period*, comparable to the usual pulse-rate in any given individual, though apparently quite classifiable with similar instances in the same type of persons

That the drop is in some way directly connected with the phenomena of sleep is apparently suggested by the fact that in our groups, when the patients were not allowed to sleep, the pronounced fall does not take place although a certain drop occurs perhaps as a result of posture or rest This conclusion is based on a study of sixty cases Furthermore, when sleep is disturbed, as by disagreeable dreams, noise or pain, although complete unconsciousness may be attained the drop is not so pronounced This fact may very likely account for the comparative exhaustion which

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5 Quoted by Theodore Janeway "A Clinical Study of Blood Pressure"

is clinically observable in patients after a night of disturbed, although unconscious, sleep. This fact was especially suggested by one night's observations when the sleep in the general ward had been disturbed by the presence of a delirious patient. Records taken of previously studied patients, who despite the annoyance had become unconscious, showed a drop, but not to the accustomed degree.

Disturbance of patients during the first sleep delays, but does not necessarily prevent the maximum fall in pressure, but frequent interruption of sleep does prevent it. When the maximum drop has taken place before the patient wakes it does not recur that night no matter how sound the subsequent sleep may be.

As to whether this drop is occasioned by the sleep or whether it occurs as a rhythmic phenomenon, independent of, but concurrent with sleep, we do not as yet feel entirely prepared to speak, but we do not think from our studies that it is in any way concerned in the causation of sleep, for the fall appears subsequent to, rather than preliminary to, or concurrent with sound sleep. As some of our instances apparently show, sleep, sound, refreshing, at the usual time and apparently entirely physiological, may occur without this drop, we are nevertheless convinced that in general the drop is a physiological necessity and that its degree is determined in at least a general way by the requisite rest and release from tension demanded by the individual.

The amount of night urinary secretion is apparently in no way dependent on the grade or degree of pressure-drop in so far as can be determined from these cases. (Six cases only were studied in regard to this point, two high, two medium and two low.)

In an attempt to apply these observations clinically we have endeavored to ascertain whether prolonged sleep causes a proportionate lowering of the pressure. Within an ordinary degree at least this does not appear to be the case and attempts to secure even a temporarily lower twenty-four-hour pressure by prolonging or deepening the sleep were apparently without avail. Furthermore, we found that little difference existed in the total twenty-four-hour pressure whether the patient is confined to bed or is allowed to be up and about.

A special series of observations (ten instances) were conducted to determine whether the sleep drop might not be artificially increased in order to secure a lower pressure curve in concrete cases of high pressure. We obtained no results in this direction and in cases in which the drop and curve had been previously determined, by the administration of potassium bromid in a dosage of as high as 120 grains the degree or persistence of the fall was not increased. The same lack of result was shown when chloral hydrate in a dosage of 50 grains per night was given.



yet the drop and curve were not materially altered. From these and from other clinical observations we feel justified in the discouraging conclusion that this sleep-drop cannot as yet be utilized therapeutically to lower the blood-pressure and that although its effect in high blood-pressure cases is more marked than that of any drug in medicinal doses, it cannot be employed therapeutically. It may, however, be said parenthetically that the more we study this question of blood-pressure the more we become persuaded toward the conclusion that the often frantic efforts to lower high blood-pressure are perhaps as harmful, if successful, as they are usually futile.

44 West Ninth Street—84 West Twelfth Street

ARTERIAL LESIONS FOUND IN PERSONS DYING FROM  
ACUTE INFECTIONS, AND ATTEMPTS TO PRO-  
DUCE ARTERIAL LESIONS IN ANIMALS  
BY NON-INFECTIOUS TOXINS \*

CHANNING FROTHINGHAM, JR., M D  
BOSTON

In a former study<sup>1</sup> it was shown that diffuse arterial lesions of a mild grade were frequently associated with certain acute infectious diseases in young people. These lesions were in no way characteristic of acute infections, as they were similar to the usual lesions found in the arteries in old age, whatever be their causes. These lesions consisted of fatty changes with or without cellular invasion in the intima and media of the vessels. In some cases the connective tissue was increased in the intima, media or both, and in some there was loss of muscle substance in the media. In the arteries in the spleen there was a peculiar hyaline-like degeneration involving one or all the coats. It is impossible to say, therefore, whether or not these lesions in these special cases are due to the toxins of the disease.

In one of the cases of general septicemia in this former study a different kind of arterial lesion was found in the kidney. There was necrosis of the vessel wall with fibrin formation and invasion into and around the vessel wall of polynuclear leukocytes and endothelial cells, as is shown in the accompanying photograph.

It is known that the tubercle bacilli and the spirochetes of syphilis invade arterial walls and cause lesions characteristic of the organism, which leave a permanent scar. The question therefore arose as to the possibility of this lesion being due to the presence of some special infectious organism, or to a certain kind of circulating toxin.

This study consisted of a search for lesions of this type. For this purpose autopsy material, preserved in the usual routine manner of the Boston City Hospital pathological laboratory, was used. The tissue after Zenker's fixation was stained with eosin and methylene-blue stains. Sections from the more important organs and aorta were examined. Occasionally one or more organs were missing in a given case. Usually only one or two slides of the same organ were examined. This was found later

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\*From the laboratory of the Department of Theory and Practice of Physic, Harvard University

1 Frothingham THE ARCHIVES INT MED, 1911, viii, 153

to have been unfortunate as in some cases lesions would only appear in every third or fourth slide

As this type of injury to the vessel wall was quite distinct from the early or late so-called arteriosclerotic changes, tissue from patients up to 40 years of age was studied. In all, sections from fifty-six patients were examined. Of these forty-eight died from acute infectious diseases. These forty-eight cases included bronchopneumonia, diphtheria, typhoid fever, pneumonia, tuberculosis, scarlatina, measles, general sepsis, and septic conditions of the ear, salpinx, peritoneum, meninges, joints, brain, liver and pleura.

No mention will be made of the lesions in the vessels characteristic of so-called arteriosclerosis and occurring in cases of acute infection as described above. Only those lesions are mentioned in which there was necrosis of the vessel wall with fibrin formation and cellular invasion. In some of these vessels thrombi were formed which extended beyond the site of the necrosis. In none of the eight cases which died from chronic non-infectious disorders were lesions of this type found.

Of the forty-eight cases with acute infections eight showed arterial lesions of this type. These cases with the location of the lesions were as follows:

Artery in the kidney from the case numbered Path Records 1910 15. For this photograph I am indebted to Dr F B Mallory.

Pathological record B C H 1911 47, aged 6 years. Purulent meningitis. Autopsy cultures, streptococcus. Arteries in meninges involved. Arteries in other organs not affected.

Path record B C H 1911-38, aged 32 years, tuberculosis of lung and meninges. Autopsy cultures, tubercle bacilli, and mixed growth. Only meningeal vessels show this lesion.

Path record B C H 1911-42, aged 34 years. Acute endocarditis, pneumonia, pulmonary infarcts. No culture taken. This type of arterial lesion occurred only in the lung.

Path record B C H 1911-4, aged 3 years. Empyema and lung abscess with miliary tuberculosis following scarlet fever. Autopsy cultures showed mixed infection. Acute arterial lesions of this type found in liver and lungs.

Path record 1910 179, aged 3 years. Empyema, pericarditis, and meningitis following diphtheria. Autopsy cultures negative. This type of lesion only found in the vessels of the lung and meninges.

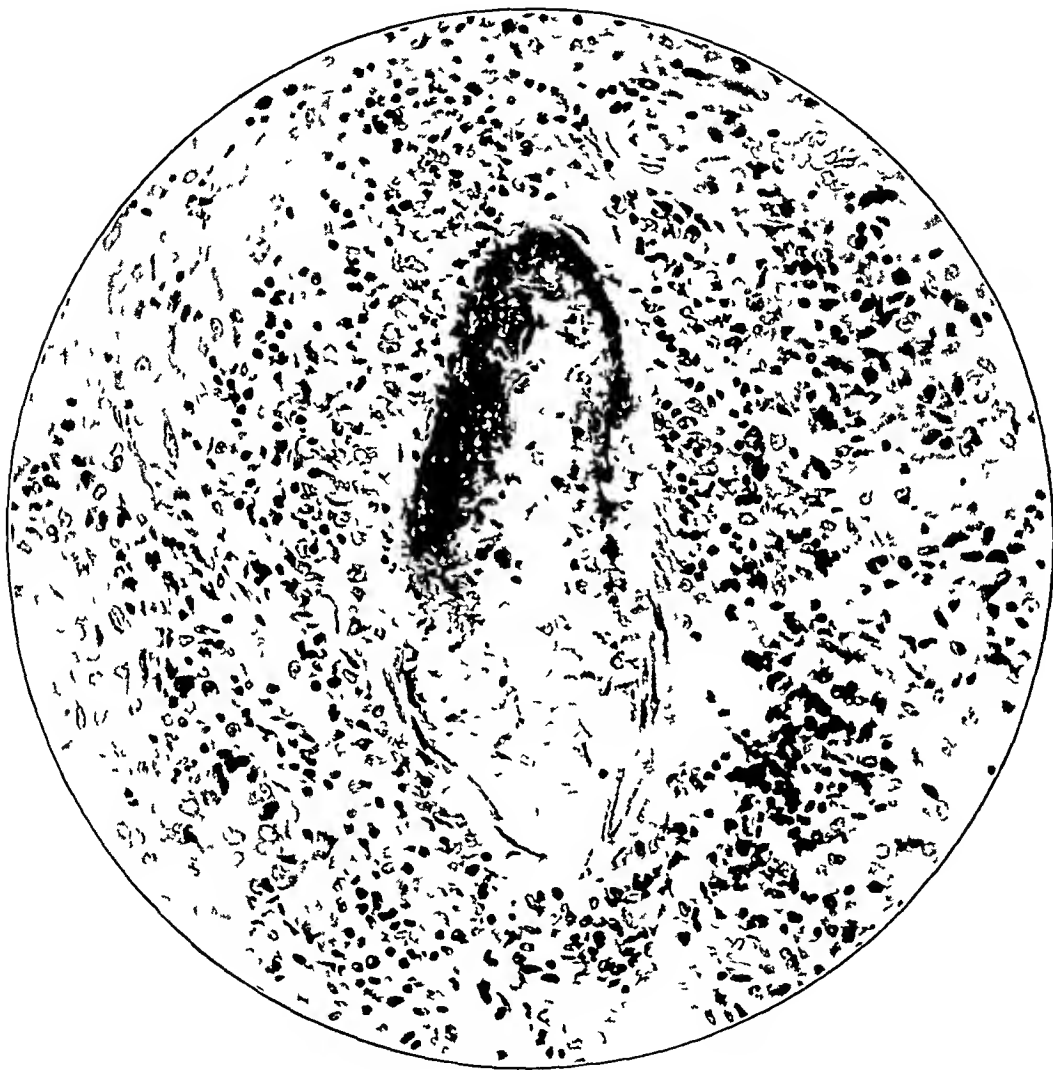
Path record 1911 96, aged 3 years. Diphtheria and bronchopneumonia. Autopsy cultures, diphtheria bacilli and others. Vessels in the pharyngeal wall showed these lesions.

Path record 1910 15, aged 8 years. General sepsis with pus in joints, etc following scarlet fever. No cultures taken. Marked arterial lesions of this type were found in the kidney, heart, liver and muscle abscess.

Path record, 1897-171, aged 3 years. Diphtheria and interstitial nephritis. Autopsy cultures streptococcus and staphylococcus. Only tissue of the kidney was available. In the kidney were marked arterial lesions of this acute type.

From a study of these cases it is evident that marked arterial lesions of this type although not common, do occur with moderate frequency and are pretty well distributed throughout the different organs. They

seem to occur chiefly in infections caused by or complicated with the pus-forming cocci. In no case could the possibility of the bacteria being present in the lesion be excluded, although they were not demonstrated. The case of periarteritis nodosa reported by Longcope<sup>2</sup> shows a similar lesion and is considered to be due to some infectious process. Recently Mallory<sup>3</sup> has found similar lesions in the arteries of the heart during acute articular rheumatism. The end-result of such a lesion on healing must show a permanent scar in the arterial wall. It seems reasonable



Marked arterial lesion found in an artery in the kidney following scarlet fever

to suppose that less severe infections of the same type which terminate in recovery may cause similar arterial lesions with an arterial scar carried into later life. The question immediately arises, Do repeated lesions of this sort lead to the so-called arteriosclerosis of old age? If such a lesion heals with a partial occlusion of the lumen, it is reasonable to

2 Longcope Bull Amer Clin Lab Penn Hosp December 1908

3 Mallory, F B Unpublished article

suppose that the vessel wall distal to this point may suffer from diminished blood-supply. It is also possible that the arterial wall adjacent to the scar may suffer from lack of nutrition due to the surrounding scar tissue.

With the hope that clinical histories might throw some light on the cause of arteriosclerosis the record of two patients with marked sclerosis of the arteries aged 22 and 16 years, respectively, were carefully studied. There was nothing in the history of either case which could be pointed to as a possible cause of the sclerosis. It is only fair to state that the histories were not carefully taken with this point in view.

In studying these sections it was noted that in cases of chronic disorders such as nephritis, diabetes, etc., the arterial lesions characteristic of arteriosclerosis were usually quite marked. An attempt was made, therefore, to produce in rabbits arterial lesions of the degenerative type by metabolic or chemical poisons.

Although the experiments were uniformly unsuccessful in producing lesions, they will be briefly described. In this work tissues preserved in formaldehyd solution, were stained with Schiavallo R for fat in addition to the routine eosin and methylene-blue stain on Zenker fixed material used in this laboratory.

Double nephrectomy under ether anesthesia was performed on five rabbits which lived from twenty-four to forty-four hours after operation. In this time fatty changes had occurred in the heart muscle as described by Lewis<sup>4</sup> but no evidence was found of lesions in the arteries.

Bovine<sup>5</sup> bile was injected intravenously, intraperitoneally and subcutaneously in varying amounts into rabbits for different lengths of time. Although the results varied with the different biles used it seemed as though fatty changes were produced in the heart and liver in some cases. No arterial lesions were formed, however, in any of the cases. Tissue from a cat which had been kept in a state of glycosuria for over a year by Dr. Allen was examined for fatty changes in the vessels. No pieces of the aorta were obtainable but the arteries in the different organs showed no degenerative lesions.

The kidneys were examined in four rabbits which had been injected by Dr. Christian<sup>6</sup> with mannium nitrate and either caffeine or adrenalin and spartein in work on experimental nephritis. In these kidneys marked lesions were found in the parenchymal cells and also in the glomeruli. Hemorrhages were present in the glomeruli. In three of these cases no arterial lesions were found. In one a few fat granules were present in a few of the small arteries.

4 Lewis Jour Med Research 1907 viii 291

5 Frothingham and Minot Jour Med Research 1912 viii

6 Christian, Smith and Walker THE ARCHIVES INT MED, 1911, viii, 468

In three rabbits which had been injected with adrenalin and spartein by Dr Christian there were marked degenerative lesions in the cardiac muscle and proliferation of the cardiac connective tissue. In these cases the arteries showed no lesion with the possible exception of a slight amount of fat in a few arteries in one case. It is interesting to note that toxins, which will produce an hypertrophy of connective tissue in the stroma of an organ apparently have no effect on the connective tissue of the vessel walls.

#### CONCLUSION

Although this study has thrown no light on the relation between non-infectious toxins and arterial disease it has shown that during acute infectious diseases severe localized arterial lesions may occur.

51 Hereford Street

# SOME CLINICAL AND EXPERIMENTAL OBSERVATIONS WITH A SACCHAROMYCETE \*

LORENA M BREED, M D  
POMONA, CAL

## INTRODUCTION

My object in presenting this paper is to relate the facts in connection with my observations and to call attention to the possible significance of yeast organisms in the sputa of doubtful lung cases

I am greatly indebted to the physicians of Pomona who have so kindly and generously cooperated with me in these investigations, and to Dr Charles C Browning of Los Angeles for consultation and suggestions in Case 7, to Dr D J Davis of St Luke's Hospital, Chicago for his interest and valuable suggestions, and also to Dr I C Herb of the Rush Medical College for assistance in translation of literature. I desire to express my deep appreciation for the ever ready and helpful interest shown by Dr Stanley P Black of Pasadena, whose wise counsel and advice have been a constant incentive to careful work.

## LITERATURE

Claude Bernard,<sup>1</sup> the French physiologist, experimenting with yeast in 1848, produced infections in animals. Since that time various observers have had similar results, using for their experiments wine yeasts, beer yeasts and the thrush fungus. Sanfelice,<sup>2</sup> experimenting in 1895 with two varieties of saccharomyces, one from fruit juice, found them to be pathogenic for guinea-pigs and white mice. Lydia Rabinowitch<sup>3</sup> made a careful experimental study with forty yeasts which were obtained from different sources. She found eight pathogenic, some producing granulomatous nodules and others a septicemia. Maffucci and Sirleo<sup>4</sup> found that a species of saccharomyces produced in guinea-pigs a pulmonary affection which resembled tuberculous pneumonia. Demme's<sup>5</sup> *Saccharomyces ruber*, which he held responsible for an outbreak of intestinal catarrh in a family of seven children, was found to be pathogenic for guinea-pigs, dogs and mice.

That saccharomycosis of the mucous membrane is possible has been demonstrated by Colpe<sup>6</sup> and Bosdike who obtained a pathogenic yeast

\*Manuscript submitted for publication May 21 1912

\*Read at the meeting of the Southern California Medical Society at Pasadena, May 1 1912

1 Bernard, Claude. Lecons de Pathologie Experimentale, 1871

2 Sanfelice Francesco. Centralbl f Bakteriol, 1895, VIII 52

3 Rabinowitch Lydia. Ztsch f Hyg u Infektionskrankh 1895, XVI

4 Maffucci A and Sirleo L. Policlinico 1895 p 138

5 Demme R. Berlin 1890 Hirschwald

6 Colpe Aren f Gynäk, 1894, XLVII

from a patient with chronic catarrh of the uterine cervix. Busse<sup>7</sup> found the fungus in proliferative catarrh of the nasal mucosa. Busse also, in 1894, described a yeast which he found in a case of pyemia and which he named *Saccharomyces hominis*. In all he published four communications regarding this fungus and the same organism was described by Buschke.<sup>8</sup> Gilchrist<sup>9</sup> described a pure skin disease caused by a yeastlike fungus. Curtis<sup>10</sup> published an account of a case in which a yeast caused myxoma-like tumors. He called this fungus *Saccharomyces humane*. Huebner<sup>11</sup> found a saccharomycete in pustules of the skin on various parts of the body. Coiselli and Frisco<sup>12</sup> cite a case in which nodules were seen in omentum and mesentery. In this case yeast organisms were found in chylous and ascitic fluids obtained by exploratory puncture during

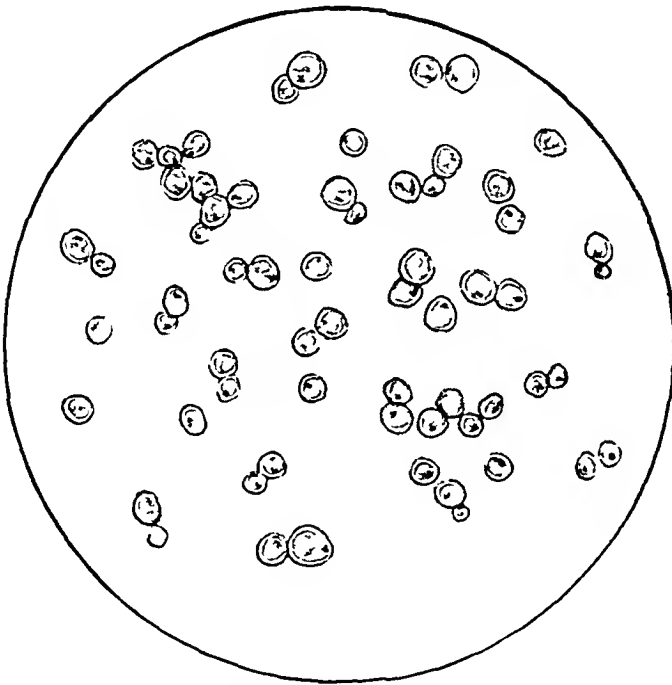


Fig. 1—Saccharomycete in fresh drop. Oil immersion.

life, and were found to be pathogenic for guinea-pigs, rabbits and dogs. Troisier and Achalme<sup>13</sup> found a saccharomycete in a case of pseudo-membranous angina in a typhoid fever patient. Clinton Hickey<sup>14</sup> of

7 Busse, Otto. Ueber *Saccharomycosis hominis*, Virchows Arch. f. path. Anat. 1895, cxl. 23. Experiment. Untersuch. uber *Saccharomycosis*, Virchows Arch. f. path. Anat. 1896, cxliv. 360.

8 Buschke, A. Klin. Wochenschr. 1898, No. 218.

9 Gilchrist, T. C. The Johns Hopkins Hosp. Rep. 1896, i. 269.

10 Curtis. Contribution à l'étude de la *Saccharomycose humaine*. Ann. de l'Inst. Pasteur 1896, v. 449.

11 Huebner. Deutsch. med. Wochenschr. 1904, Nos. 33 and 34.

12 Coiselli, G. e. Frisco, B. Centralbl. f. Bakteriologie 1895, xiii. 368.

13 Troisier, E. and Achalme, P. Arch. de méd. expér. et d'anat. path. 1895, v. 29.

14 Hickey, Clinton. Colorado Med. Jour., 1900, vi, No. 2, p. 485.



Denver described in 1900 two cases of scarlatinal angina and one of "sore throat" in which a dense exudate covered tonsils, pillars of fauces and margins of soft palate. The city bacteriologist reported "no Klebs-Löffler bacilli, no streptococci, and no staphylococci, but numerous yeast cells." Steinhaus<sup>15</sup> found a yeast in a child suffering from scarlet fever which he called *Saccharomyces membranogenes*. On the fifth day the

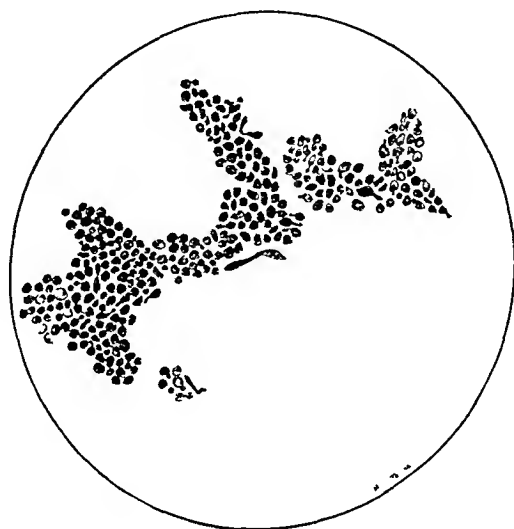


Fig 2—*Saccharomycete*, smear from 24 hour culture, stained with Löffler's methylene blue. Oil immersion

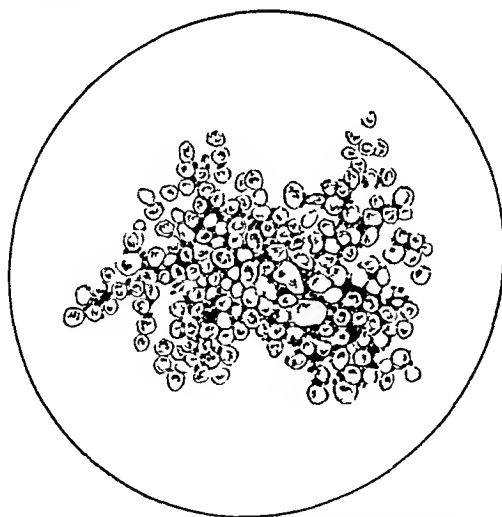


Fig 3—*Saccharomycete*, smear from 3 weeks old culture showing many empty capsules, stained with Löffler's methylene blue. Oil immersion

child developed croup with a very fetid odor. On the twenty-first day dyspnea developed and tracheotomy was performed. After operation the child coughed up a tenacious mass following which breathing became

<sup>15</sup> Steinhaus. *Centralbl f Bakteriol I abt Orig*, 1906 07, xlii part 1, p 49

easier. An aseptic instrument was passed into the trachea and membrane secured for cultures. One thousand units of antitoxin were given, as diphtheria had been diagnosed. The patient died next day. Autopsy was not allowed. Cultures were made on Löffler's blood-serum. Sixteen hours later the plate showed large, glistening, round, light yellow-tinged colonies which, much to his surprise, revealed pure cultures of yeast.

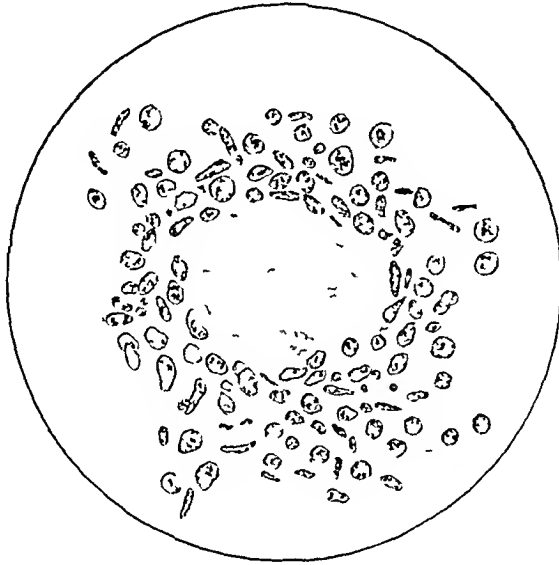


Fig 4—*Saccharomycete* in tissues, surrounded by leukocytes, mostly polynuclears, hematoxylin and eosin stain. Oil immersion.

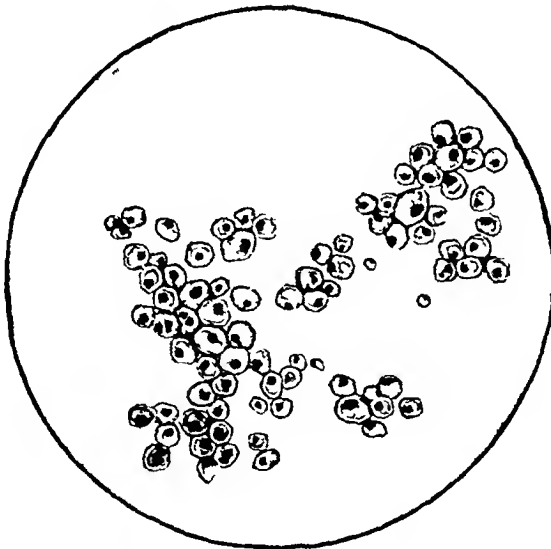


Fig 5—*Saccharomycete* nuclei stain Janssens and Leblanc's modification of Mueller's method. Oil immersion.

In his animal experiments, mice, guinea-pigs and rabbits were employed. He used intravenous, subcutaneous and abdominal injections, also feeding bread soaked in bouillon cultures of yeast, all of which produced the characteristic infection, and at autopsy the characteristic miliary tubercles

and sections revealed the yeast fungus in all organs and in blood-vessels and nerves. His article is complete in every detail. Reitman<sup>16</sup> cites a case, a patient of 30 years, sick eleven days, who died four days after entrance to the hospital. The autopsy showed ecroupous pneumonia and glomerulitis. Only sections of kidneys were examined, but many of these sections contained double-contoured refractile bodies between 5 and 20 microns found in epithelium of the tubules in the glomeruli, and free in the blood-stream. It was impossible to make cultures in this case on account of the non-recognition before hardening. He depended on staining and morphology, but thinks that they correspond to the organism described by Busse. Castellani,<sup>17</sup> director of the Clinic for Tropical Diseases, Colombo, gives some interesting observations on fungi found

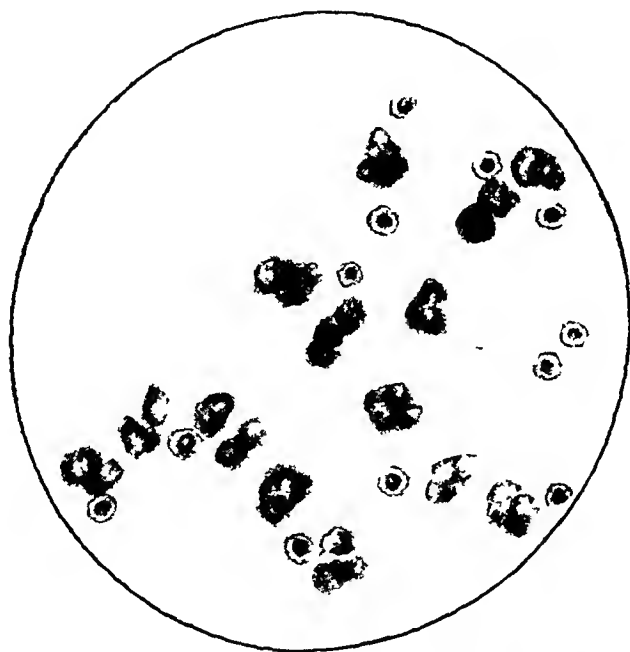


Fig. 6—*Saccharomycete*, smear from pus in Case 14, nuclear stain for differentiating. Oil immersion.

in tropical bronchomycoses, to which various names are given (tea-factory cough, copra cough, etc.), Among other fungi he found a *saccharomycete* twice.

The subject of pathogenic yeasts has been so carefully and thoroughly covered, and the literature so completely reviewed by Ricketts in his monograph "*Oidiomycosis (Blastomycosis) of the Skin and Its Fungi*" and by Hektoen in his summary of cases of "*Systemic Blastomycosis and Coccidioidal Granulomata*" that further reference except to these two

<sup>16</sup> Reitman. *Centr. bl. f. Bakteriol.*, 1895, p. 225.

<sup>17</sup> Castellani, Aldo. Observations on the fungi found in the Tropical Bronchomycoses. *Lancet*, London, 1912, No. 1, p. 13.

works, with their bibliography, seems unnecessary Hektoen<sup>18</sup> says that the history of many of the cases cited by him, and the bronchopneumonic character of some, may be taken to indicate their air-borne nature In a number of these cases blastomycetes were found in the sputum, and in some of them the pulmonary symptoms were the first to appear, followed in most cases by localization of lesions

Regarding the occurrence of yeasts in Nature, Klocker<sup>19</sup> says

"Hansen's researches on the circulation of saccharomycetes in Nature, and on the amount of microorganisms in the air at various seasons of the year, have led to the following results, very important to the brewer (1) Wind and insects are the most important means of transportation of yeast cells in Nature, especially the first (2) Dust clouds in the harvest months are rich in strong yeast cells produced on sweet, juicy fruits" He describes saccharomycetes as "single cell fungi in which vegetative increase takes place by budding and which develop endospores in their interior under certain conditions, sometimes they may form typical mycelium The various related species are grouped according to their action on various sugars"

In a careful comparative study of other known cells, together with the yeast plants, Mutchler came to the following conclusions which he thought justifiable (1) Yeast-cells contain structural elements that are homologous with the structural elements of the cells of higher plants and with the known structural elements of animal cells and with the structural elements of the bacteria and the cyanophyceæ as worked out by Butchle and also by Kumbler (2) The structural elements consist of four definite regions, are found in both mature cells and in the growing buds and correspond to what is well known in the higher plants and in animal cells as cytoplasm, nuclear membrane, nucleus and nucleolus The structural elements may be demonstrated clearly by the four methods of differential staining discussed by him and are to be found in every yeast cell Emerson<sup>20</sup> says that as the presence in the sputum of certain pathogenic yeasts cannot be denied, in doubtful cases they should be looked for as a possible explanation of anomalous lung conditions Hektoen suggests further careful study of new cases both clinically and anatomically, and further observations in regard to the blood, especially to the number of leukocytes and differential counts B F Davis<sup>21</sup> of Chicago has given valuable information in immunological reactions of *oidiomycosis*

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18 Hektoen, Ludvig Jour Am Med Assn, 1907, xlv, 1071

19 Klocker "Fermentation organisms," 1903 English translation of the German edition, p 248

20 Emerson, Chas P Clinical Diagnosis, 1911

21 Davis, B F Jour Infect Dis, 1911, viii, 190

## AUTHOR'S OBSERVATIONS OF A YEAST

During more than two years of clinical laboratory work in Pomona I have encountered a yeast in fifteen individuals sent to me for laboratory diagnosis. This organism I first discovered in a vaginal discharge. Four months later I found similar organisms in the sputum of a child said to have tuberculosis, and again in a culture from the tonsil membrane of a child supposed to be suffering from diphtheria. The fourth time I encountered this fungus was in the sputum of a patient with a pulmonary lesion resembling lobar pneumonia in the early stage of resolution. In this case repeated examinations of the sputum failed to reveal any tubercle bacilli and the tuberculin test was negative. To ascertain what was causing the symptoms I made cultures from the sputum and each time got a pure growth of an organism which I identified as a *saccharomycete* and which gave the same results culturally and with animal experimentation as did the fungus found in the vaginal discharge in the first case.

After the above experience I made a routine practice of washing and examining culturally all sputa sent to the laboratory in which, after repeated examinations, I found no tubercle bacilli. As a result I have discovered a yeast organism in a number of other patients which corresponds morphologically and culturally to those found in the preceding cases. At times the organism was found in pure culture, again in connection with a staphylococcus or *Micrococcus catenulatus*, and twice it was found mixed with tubercle bacilli, but in all cases the morphological and cultural characteristics were identical, and animal experiments with the strains tested gave the same results.

*Morphology*—This organism resembles the *Saccharomyces cerevisiae* both culturally and morphologically, but the latter on all culture media grows less profusely and is less spherical. It is about the size of a red blood-corpuscle, possesses a double-contoured capsule and contains fine granules and refractile bodies like fat or vacuoles. Old cultures show lessening of granules and extension of vacuoles, and numerous empty capsules. It grows by budding and possesses a nucleus which can be demonstrated by special staining. In one old culture there was a slight tendency to form threads. I have found no endospores but have made no special cultures for spore formation.

*Staining Properties*—In smears from cultures this organism stains well with all ordinary dyes. It is Gram positive. It is not acid fast. Direct smears from pus or thin sputum are best treated with Wright's blood stain, which colors the pus cells a pinkish purple and the yeast organisms a dark blue, while the red blood-cells are a brick red. For staining the nucleus I have used Janssen's and Leblanc's modification of Mueller's method as used by brewers, the technique of which is given in "Klocker's Fermentation Organisms." This requires four days but is

excellent for differential purposes. It stains the nucleus a dark red and the cytoplasm a pale pink.

*Cultural Characteristics*—On glucose and glycerin-agar slants there is a profuse creamy growth at 37 C in twelve to twenty-four hours. On potato slants but a slight film in the same length of time. It turns litmus milk a full creamy white in twenty-four hours with formation of a soft curd. It grows vigorously on both plain and glucose bouillon, forming a heavy sediment in the bottom of the tubes, and in the latter the appearance of foam on shaking. There is a profuse growth on both plum and grape decoctions but no foam on shaking the tubes. It does not liquefy gelatin, but growth appears along the line of the stab with roseate formation at the top. Agar plates reveal white moist points in twenty-four hours. On all culture media there is but slight growth at room temperature. The minimum temperature for visible growth of this organism is 18 C and the maximum temperature is 69 C. It is devitalized at 71 C for one hour. Two-year-old cultures which were quite dry were moistened with salt solution, and from them fresh culture media inoculated. A fairly vigorous growth resulted. Glucose is fermented, giving rise to alcohol and carbon dioxide. Growth occurs in lactose, dextrose, raffinose, inulin and mannite in 2 per cent solution, though there is no evidence of fermentation. On all culture media this organism gives rise to the characteristic odor of yeast. Plates continually exposed in the laboratory reveal no growth of this fungus.

*Animal Experiments*—This organism is pathogenic for rabbits, white rats, guinea-pigs and monkeys. Subcutaneous injections produce slowly developing septic conditions from which the animals tend to recover if not injected too often. Intraperitoneal injections produce in guinea-pigs and white rats a rapidly fatal septicemia, in rabbits and monkeys within a few weeks rapid loss of weight and more slowly developing septicemia. In all animals within a few hours after intraperitoneal injections there is rapid breathing, high temperature and some leukocytosis with slight increase of mononuclear cells. Autopsies without exception reveal grayish milky tubercles thickly studding all internal organs, and peritoneal and pericardial surfaces. Sections of these tubercles show masses of the yeast-cells, surrounded by leukocytes, mostly polynuclears. The organism was recovered in pure culture from the heart's blood, bile, peritoneal and pericardial fluids and the milky tubercles, and direct smears showed full-grown and budding yeast cells.

#### HISTORIES OF CASES IN WHICH THE ORGANISM OCCURRED

CASE 1—Physician, Dr. Huntington, patient J. H. aged 11. The patient came under observation Dec. 4, 1909. Four months previously while swinging on a rope she lost her hold and slid down to the knotted end receiving injuries about

the external genitals When first seen the labia were red, smooth, shining and sore, small whitish patches thickly covering the parts These lesions which, when first seen, were confined to the external genitals, later invaded the vaginal tract The whitish patches rapidly coalesced and formed a clinging membrane, and if not treated frequently the underlying parts became highly inflamed and very sore When daily treatments were given, cultures showed feeble growth, but if three or four days elapsed between treatments, cultures yielded vigorous growth From December, 1909, until March, 1910, daily and often twice daily treatments were given From March until July laboratory examinations were continued at intervals, but during this period there was no reappearance of the patches, or growth on culture media, although the parts remained red and shining In July the characteristic whitish patches were again observed on the inflamed parts and a culture taken revealed a profuse growth of the yeast in twelve hours It was a problem to find a solution of anything strong enough to affect the growth without irritating the mucous membrane Weak solutions of mercury chlorid, copper sulphate, ichthyol and boric acid all caused pain Various powders proved inefficient Cleaning the parts with sterile water, using gentle friction, gave best results Douching the parts with sterile water without friction had no effect The patient had little systemic affection The cervical glands were slightly enlarged, but there was no elevation of temperature, the patient gained in weight during the treatments Late in July the family removed to Oregon and two months later the father of the child reported that there was no further trouble

CASE 2—Physician, Dr Toland, patient, a 4 year old son of Mrs T The mother in April, 1910, consulted Dr Toland about the child, who was coughing excessively This case had been pronounced tuberculosis by her former physician In the sputum sent to the laboratory for examination I found a yeast, but no tubercle bacilli The mother left town soon afterward and the child was not heard from again until December, 1911 The cough was still present, but the child had improved physically

CASE 3—Physician, Dr Toland, patient, W M S, business man, aged 36 The patient came under notice in 1910 with pharyngitis He had lost in weight slightly and feared tuberculosis The tuberculin test was negative, repeated examinations of sputum covering a period of several months failed to reveal tubercle bacilli Cultures from sputum yielded pure growth of a yeast The cough continued to be troublesome for more than a year but by November, 1911, it had entirely disappeared

CASE 4—Physician, Dr Savage, patient, a girl of 10 years, with a history of chronic enlargement of the tonsils for two years, which, when first seen, were soft and boggy, associated with acute inflammation of the entire throat, and dense yellow patches confined to the tonsils From a detached piece of membrane sent to the laboratory a culture revealed a vigorous growth of a yeast but no Klebs-Löffler bacilli While waiting for the laboratory diagnosis intubation was given, but the membrane continued to form and three weeks later intubation was performed The child made a good recovery

CASE 5—Physician, Dr Swindt, patient, Mr H V S, aged 56, a rancher This patient was first seen in June, 1910 Two weeks before coming under notice he had a severe "cold" and cough, with viscid, blood streaked sputum At the time of entrance to the hospital he had chills, sweats and a temperature of 102 F At the base of the left lung were detected signs of lobar pneumonia undergoing resolution The blood and urine were normal The tuberculin test was negative, and frequent examinations of the sputum revealed no tubercle bacilli, but cultures from the sputum resulted in a pure growth of a yeast Large doses of sodium iodid were given and within two weeks the pulmonary symptoms had entirely disappeared Phlebitis of the left leg occurred while in the hospital, and lasted for about three weeks The patient reported, Jan 15 1912, that there was no cough or other pulmonary symptoms The left leg swelled some when he worked hard

CASE 6—Patient, M H, servant girl, aged 22 This patient was sent directly to the laboratory for a sputum examination by her employer, on account of a constant cough She had come to California during the early summer on account of "catarrh" Her general health improved but the cough persisted Repeated examinations of sputum failed to reveal tubercle bacilli The tuberculin test was negative and the blood was normal Cultures from the sputum yielded an almost pure growth of a yeast Her employer advised her to seek another position and she took service in a mountain resort, but the high altitude did not agree with her and she went to Long Beach Information from her first employer in November, 1911, was that she had entirely recovered

CASE 7—Physician, Dr Browning, patient, Mrs E D C, aged 35, married The patient came from Idaho to southern California on account of persistent cough which dated from an attack of bronchitis in March, 1910, from which time she complained of a pressure over the chest and a difficulty in breathing She had a loose paroxysmal cough with a profuse mucopurulent expectoration which was discharged after violent effort There was a moderate degree of emaciation Temperature was 99 F, pulse 100 The appetite was good and the digestion fair The right side of the chest was normal, with dulness over entire left chest and especially pronounced over the third rib Sputum examinations at intervals of from two to four days from January until May, 1911, failed to reveal tubercle bacilli The tuberculin test was negative Frequent cultures from the sputum always yielded a pure growth of a yeast and in a blood culture (bouillon) the same organism was found Autobacterins of the yeast were given at seven day intervals for six weeks, also various preparations of the iodids The patient gained in weight and improved markedly, and in cultures from the sputum the growth of the yeast organism gradually disappeared April 23 she took a long auto ride, during which she became overtired and thoroughly chilled This resulted in an elevation of temperature (104 F) and great prostration, and thereafter tubercle bacilli were observed in every specimen of sputum examined As soon as the patient was able to travel again she went east and died six months later

CASE 8—Physician, Dr Davis, patient, Miss V H, aged 19, a student In June, 1909, this patient came under observation with a laryngitis which did not yield to treatment Examination of the lungs revealed a small area of infiltration, in which occasional moist râles were heard, just external to left sternoclavicular articulation The morning temperature ranged from 96.6 F to 100.2 F. Afternoon temperature ranged from 101 F to 104 F There was a troublesome cough and a profuse expectoration, also gradual loss of weight and night sweats In November, 1909, a sputum examination revealed tubercle bacilli mixed with pus organisms Tuberculin was not given until December, 1910, from which time this treatment was continued until March, 1911, but the temperature remained high and the patient was losing ground At this time the sputum was sent to my laboratory with a view of having an autobacterin prepared for the mixed infection Sputum examinations revealed very few tubercle bacilli Cultures revealed a luxuriant growth of a yeast, with *Staphylococcus aureus* The tuberculin was discontinued and an autobacterin of the yeast organism given every seven days for six weeks The afternoon temperature gradually but steadily decreased but never at any time became normal During the same time the yeast growth decreased until there was scarcely anything visible on culture media in twenty-four hours The patient's general health, however, did not improve and she died May 29, 1911 There was no autopsy

CASE 9—Patient, Miss V R, school girl, aged 16 This patient was almost a constant companion of the 16-year old daughter of the patient, Case 7 She was sent directly to the laboratory by her mother for a sputum examination because of a constant, distressing cough A sputum examination revealed no tubercle bacilli and the tuberculin test was negative In a culture from the sputum pure growth of a yeast resulted Potassium iodid, 10 grains three times daily, caused the cough to disappear entirely within a few weeks



CASE 10—Patient, Mrs R, seamstress, aged 51, mother of patient Case 9, developed a cough soon after the daughter. All of the findings were exactly as in Case 9, but the cough was more persistent and she was obliged to keep up the iodids longer and in much larger doses. Eight months later both patients were entirely well.

CASE 11—Physician, Dr Swindt, patient, Mr C H A, clerk, aged 55. This patient had a chronic bronchitis for thirty years, but his general health was good up to five years previous to examination. During the previous five years he had occasional fever and frequent attacks of hemoptysis, but never any marked loss of weight. He had profuse fetid expectorations for the previous four years. There were signs of chronic bronchitis in both lungs. The fetor disappeared under sodium iodid, and creosote reduced the amount of expectoration. In April, 1911, a blood examination was negative, a tuberculin test negative and there were no tubercle bacilli found. A culture from the sputum revealed a yeast with *Staphylococcus albus*. An autobacterin of the yeast organism caused an exacerbation of symptoms which alarmed the patient and the dose was not repeated. Patient went east in May of the same year. A few months later he reported that he was taking staphylococcus vaccine (stock) without improvement. This patient had frequent sputum examinations during the past five years and tubercle bacilli were never found. An unidentified organism, however, had been reported once.

CASE 12—Physician, Dr Swindt, patient, Mrs J B P, aged 67. This patient had chronic cough for many years. During the previous four years she suffered greatly from paroxysms resembling pertussis. Her general health was good. Both lungs showed signs of moderate bronchitis. No tubercle bacilli, but pure culture of a yeast from the sputum. The paroxysms were completely relieved and the cough reduced to a minimum in about three weeks by the use of sodium iodid in large doses.

CASE 13—Physician, Dr Garcelon, patient, W S, aged 47. This patient was in the hospital with typhoid fever, and in a culture from the feces, in connection with the typhoid bacilli, a yeast was found. The patient died after a two months' illness. No autopsy. As this yeast organism resembled all of the preceding ones morphologically and culturally, animal experiments were undertaken with it, and the same results obtained as in the previous cases. It was also identified as a saccharomycete.

CASE 14—Physicians, Dr Huntington, Dr Swindt, patient, Miss L T, aged 35. The patient came under observation in November, 1910. She had had arthritis deformans for ten years and the spine and large joints were stiff. Four years previously she had appendicitis, but no operation. Three years previously she had pleurisy with effusion, followed by empyema and evacuation through the left bronchus. Since then there had been a constant, profuse expectoration. At intervals of three to eight weeks there would be an enormous increase of this expectoration, when, in a short time, from 1 to 3 pints of stinking pus would evacuate through the bronchus, pouring through nose and mouth and almost strangling the patient. In February, 1911, a sputum examination revealed no tubercle bacilli, but a culture showed a yeast, together with *Staphylococcus albus* and *M. catarrhalis*. Nov 7, 1911, a sputum examination gave the same results as ten months previously, but with an increase of the yeast organism. The tuberculin test was negative, there was some leukocytosis with 82 per cent polymorphonuclears. The temperature ranged from subnormal to 103 F, pulse from 90 to 120, respiration from 18 to 26. A radiograph showed a shadow on the left side below the clavicle. November 11 the seventh and eighth ribs on the left side were resected and over 3 pints of pus removed. The lung was found in a small contracted mass high up in the cavity, with apparent communication with the bronchus. The condition of the patient did not permit of decortication. The cough disappeared and the general condition immensely improved following the evacuation of pus. In smears from the pus from the wound yeast organisms were found. Culture from the pus revealed yeast organisms in almost pure growth. An

agglutination test of the yeast with this patient's serum, 1-40 and 1-50, was strongly positive, while controls were negative. An extract of yeast made for me in the Cutter Laboratory, Berkeley, according to the technic for Koch's old tuberculin, proved slightly positive in a skin test, controls negative. Autobacterins of the yeast were begun a few weeks after the patient left the hospital and her improvement has been uninterrupted.

CASE 15—Physician, Dr. Kelly. The patient, Miss A. C., aged 15, school girl, had always been subject to "colds." She came under notice in December, 1911, with a severe cough. The mother of the child said that cough and expectoration had been continuous for the previous three months. There was some loss of weight and some anemia. The temperature was 99 F, pulse 90, blood examination showed hemoglobin 50 per cent, red blood-cells 80 per cent, no leukocytosis, polynuclears 83 per cent, tuberculin test negative. An examination of the sputum every day for two weeks revealed no tubercle bacilli. A culture from the sputum showed a vigorous growth of a yeast with *Staphylococcus aureus*. An agglutination test with the yeast was slightly positive, controls negative. The patient refused to have a skin test with the yeast extract. Large doses of sodium iodid were given.

The above histories are not complete, but abstracts as given me by the physicians in whose service they occurred.

#### NOTES ON CASES

In few of the cases herein cited have we had opportunity for careful clinical study. Only two of the patients were in the hospital at all and then for only a short time. The organisms from Cases 1, 4, 5, 7, 8, 13, 14 and 15 were employed in animal experiments with practically the same results. In Case 1 we were not allowed to make a skin test or blood examinations, but the clinical picture was observed closely. In taking smears or cultures here, the parts were always cleansed first with sterile water. It was significant that with the disappearance of the yeast fungus in this case the trouble disappeared entirely. Case 2 we had an opportunity of observing. Case 4 suggests cases cited by Hickey and Steinhaus in the literature, inasmuch as a tenacious membrane formed and reformed, and that there was an absence of the Klebs-Löffler bacillus. As Case 5 was in the hospital I made frequent blood and sputum examinations, but at that time had not begun making the skin and agglutination tests with the yeast. However, the absence of any organism except this fungus suggested the iodids. There was no opportunity to observe Case 6 after the laboratory analysis and it was only through the kindness of her first employer that we learned of her present condition. In Cases 7 and 8 tubercle bacilli were found mixed with the yeast organisms, but it would seem to be a secondary invader in the former while probably in the latter the tuberculous infection was primary. Both of these patients died but as there was no autopsy in either case there can be no definite knowledge regarding this. It is however significant that both of these patients were benefited by autobacterins and iodids. The facts in Cases 9 and 10 suggest that this organism may be transferred

from one person to another. The suspension of yeast organisms prepared for Case 11 was kept at a temperature of 70 C for one hour, as the previous ones for Cases 7 and 8 had been, and as a twenty-four-hour culture taken from this emulsion was sterile, the dose was then given. After forty-eight hours, however, the culture tube revealed a slight growth of yeast. This undoubtedly accounted for the exacerbation of his symptoms.

Case 12 was remarkable in that it was an unmixed infection of yeast, and that it was so quickly and entirely relieved by the iodids. Case 13 was not observed with regard to the yeast organism found. We isolated and identified it simply because it resembled the organisms previously identified as *saccharomycetes*. We had more opportunity for careful study of Case 14, and the observations were fairly satisfactory. The very positive agglutination test, the slightly positive skin reaction, together with the occurrence of the same organism in the pus from the wound that I had previously and repeatedly found in the sputum, are suggestive of the pathogenicity of the *saccharomycete* in this case. Case 15 had only begun to improve with the iodids when she began taking a patent medicine and was lost sight of. In all of these cases the physicians have remarked the unusual fetor and viscid character of the sputum and repeated attacks of "colds."

The examination of the sputum requires some care. It should be washed in normal or tenth-normal sodium or potassium hydrate, and cultures made from the parts resembling pus. Smears should be treated as described above. If the sputum is to be examined unstained it should be covered with a normal solution of sodium or potassium hydrate, and allowed to stand for at least thirty minutes to dissolve the mucus. The yeast cells being resistant to the action of the alkali can easily be found and are not confused with red blood-cells.

This report leaves much to be desired in the way of clinical observation of cases, and autopsy records in cases of death, also blood examinations, especially in cases in which the *saccharomycete* is the only organism found. The complement deviation test should also be made in connection with the agglutination and skin tests. Animals should be immunized and agglutination tests made with their sera.

Five other patients are still under observation in whom a yeast has been found. One is a child aged 4½ years with repeated attacks of bronchitis followed by asthma. It has been impossible thus far to secure a satisfactory specimen of sputum, as she swallows it, but a yeast has been found in a blood culture (agar plate), also in a culture from the feces during one of her attacks of bronchitis, and her serum agglutinates the yeast organism. A skin test has not yet been made. An old lady of 79 has had ulcers on parious parts of her body for eight months past.

Yeast cells were found in the pus from one of these ulcers and could easily be recognized both in unstained and stained specimens. The remaining three patients have a severe cough, and a prominent feature is the profuse fetid expectoration and the frequent attacks of "cold." We are hoping for something more definite from the study of these cases.

#### SUMMARY

A yeast which has been identified as a saccharomycete has been observed in the sputum of a number of patients with anomalous lung conditions, also in a tonsil membrane, a vaginal discharge and in pus from a skin abscess. It was mixed with other organisms in most cases, but has been found as the only apparent cause of infection in a few patients in whom disappearance of the organism has been followed by alleviation and disappearance of the symptoms.

Autobacterins made from this yeast organism have seemed to cause some improvement in three cases and an exacerbation of symptoms in one.

The most benefit has been derived from the use of the iodids in large doses. An extract prepared from this saccharomycete gave a slight reaction in a skin test on two patients. The serum of four patients gave a positive agglutination test for the yeast.

242 West Holt Avenue

NOTE ON "A CASE OF PANCREATIC DIABETES  
MELLITUS" BY HERMAN O MOSENTHAL

GRAHAM LUSK  
NEW YORK

This report by Dr Mosenthal<sup>1</sup> contains a point which is not brought out in the description. If the table which gives the quantitative urinary analysis be examined, it will be found that, on those days in which protein and fat were given to the diabetic individual and carbohydrates rigidly excluded, the D N ratios were respectively 3.75, 3.85 and 3.44. Thus on May 19, with a total excretion of 27.7 gm of nitrogen, the D N ratio was 3.75, and on May 24, with a total excretion of nitrogen of 11.8 gm, the D N ratio was 3.85. It is also noticeable that the ammonia excretion remains comparatively low on these days, 2.9 gm on one day and .9 gm on the other day.

These conditions are very like those in the case reported by Mandel and Lusk<sup>2</sup>. At the time of their investigation, they termed the ratio 3.65 the fatal ratio, a condition in which combustion of carbohydrates is essentially impossible. Since clinicians in general have hesitated about withdrawing carbohydrate completely from the diet of diabetics, there are few cases on record in which the results of Mandel and Lusk have been confirmed. It appears, however, from this work of Dr Mosenthal that, if the ammonia excretion remains low — which, of itself, indicates that the acidosis is not high — then one may, during a short period at least, withdraw carbohydrate completely from the diet and determine the D N ratio without injury to the patient.

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1 THE ARCHIVES INT MED, 1912, ix, 339

2 Deutsch Arch f klin Med, 1904, lxxvi, 472. For further information consult Lusk, Jour Am Med Assn, 1904, xliii, 241, and 1910, lv, 2105. THE ARCHIVES INT MED, 1909, iii, 1, Science of Nutrition 1909, p 299.

## PELLAGRA IN ILLINOIS

### CONDENSED REPORT OF THE ILLINOIS PELLAGRA COMMISSION<sup>1</sup>

In this report the results of the various investigations which have been undertaken, together with those reported to this Commission by other observers, have been incorporated in one article. The material has been to some extent condensed and summarized in order to eliminate unnecessary details, which can be found by those interested in the detailed report made to the Governor of Illinois. This detailed report will be published shortly in the form of a monograph and copies sent to all important libraries in the United States.

At this point we wish to express our acknowledgments to those who have so materially helped in the compilation of this report by sending us personal communications. They include Captains J. F. Siler and H. G. Nichols of the United States Army, detailed by the courtesy of Surgeon-General Wyman, on the request of Governor Charles S. Deneen, to study pellagra in Illinois; Prof. Stephen A. Forbes, Entomologist to the State of Illinois; Dr. J. F. Waugh of Chicago; Dr. Arthur D. Hirschfelder of Baltimore, and Dr. Sidney D. Wilgus, Superintendent of the Kankakee State Hospital. We would also especially express our thanks for the unfailing courtesy and assistance of Dr. George A. Zeller, Superintendent of the Peoria State Hospital, without which we should have been sorely handicapped. We have also received much assistance from other sources, and would mention especially Dr. J. T. Rooks, Mr. A. F. Wussow, Miss Josephine (Keir) Allison, Miss Mattie A. York, Dr. L. J. Pollock and Dr. C. E. Smith, who have performed a great deal of the detailed work on which this report is based.

#### I. CURRENT VIEWS ON PELLAGRA

There is no need in this report to enter extensively into the history and geographical distribution of pellagra, since many excellent treatises are available. The disease was apparently first described by the Spanish physician Casal in 1735, although this was not published until after his death in 1762. The following paragraph quoted from the monograph by the late Dr. J. N. Hyde of Chicago<sup>1</sup> will sufficiently indicate the wide distribution of the disease.

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\*Dr. Frank Billings, President  
Dr. J. L. Greene, Vice-President  
Dr. Oliver S. Ormsby, Secretary  
Dr. George W. Webster

Dr. H. S. Grindler  
Dr. Howard T. Ricketts  
Dr. H. Douglas Singer  
Dr. W. J. McNeal

<sup>1</sup> Hyde, J. N. Pellagra and Some of its Problems. *Am. Jour. Med. Sc.* Jan

Fiapoli, of Milan, in 1771, is commonly reported as first to have given the name to the disease by which to day it is most generally known, but in fact he merely reproduced a title current among the people of his day "*Morbus vulgo, Pellagra*" In the long list of authors who followed, from Strambia, Maizari, Alibert, Rayer and Raymond, to Lombroso, Sandwith, Babes and Sion, and Sir Patrick Manson, can be traced the progress of the disease in Europe from Spain to southern France, northern and central Italy, Corfu, upper Egypt and other parts of Africa, Austria, Servia, Bulgaria, Roumania, Asia Minor, India, Mexico, Barbadoes, and portions of North and South America

With regard to the etiology of pellagra numerous views have been promulgated and it is well to say that the members of this commission entered on this study without prejudice or preconceived ideas with regard to the nature of the disease or its causation The plans on which the work has been organized have been aimed towards the consideration of all the manifold theories which have been evolved in order if possible, to narrow the lines of research into some more or less definite channel The great drawback of most of the work which has so far been carried out, is that the investigator has started with some hastily-formed hypothesis, based on coincidences or chance observations which have not been submitted to careful scientific analysis He has then been only too willing to see and insist on the pellagrous nature of the most variable symptoms produced in lower animals as the result of experiments founded on such hypothesis

One of the best critical reviews of previous work on pellagra will be found in the Progress Report of the British Commission for the Investigation of Pellagra, by Louis W Sambon<sup>2</sup>, especially in regard to the relation with maize Free use has been made of this article in compiling the following statements

The various theories which have obtained may be subdivided under two main headings (1) Those concerning maize or Indian corn, (2) those alleging other causative agents The supporters of the first group are commonly known as zeists and of the second as antizeists

1 Theories which allege some causative relation between maize and pellagra have been most widely accepted, but are gradually losing ground They have been and still are almost universally believed in Italy where this disease is probably more prevalent than in any other part of the world This is largely due to the influence of Lombroso, by whom it was firmly believed and widely expounded, with the result that the Italian government was led to promulgate laws dealing with the use and care of Indian corn In fact Sambon with considerable justice points out that the Italians have been studying corn rather than pellagra

Various authorities differ in their views as to the nature of the relationship between corn and pellagra These views may be briefly classed under the following headings

<sup>2</sup> Jour Tropical Med and Hyg, 1910, pp 271, 282, 305 and 319

(a) According to Lussana, Frua and others, Indian corn is deficient in or lacks some nutrient principle necessary for health, and pellagra results from a diet consisting too exclusively of maize

As a corollary to this view should also be mentioned other conditions of malnutrition. Pellagra is unquestionably a disease which occurs most frequently among the poorer and less well-fed classes, and some have regarded it as the direct result of insufficient food. In most of the different theories malnutrition and defective hygiene are given as contributory factors

(b) Corn contains some toxic substance which, in individuals who are especially susceptible for any reason, gives rise directly to pellagra

(c) Maize undergoes some form of decomposition, as the result of the growth of bacteria, in the intestine of certain individuals. The toxins resulting from this change give rise to pellagra

As will be observed, these theories deal with maize which is healthy in itself. The following views concern maize which is damaged or spoiled in some way

(d) That healthy maize is innocuous, but that at some stage in its preparation for consumption either in the ear, when stored or after being cooked, it undergoes decomposition as the result of the growth of certain fungi. Various molds and bacteria have been isolated and incriminated by different authors, e. g., *Penicillium glaucum* (the commonest variety of mold), different varieties of *Aspergillus*, *Sporisorium maydis*, *Ustilago maydis* (smut), *Bacterium maydis*, *Bacillus pellogræ*, etc. It is supposed that toxins are produced in this process of decomposition which, when absorbed, cause pellagra

(e) That some one of these organisms, which are commonly found on molded or spoiled maize, and which may be eaten with it, directly invades the human body where it elaborates toxins causing pellagra

2 The antizeist views regard the disease as a specific infection of the body with a parasitic organism either bacterial or protozoal in character

(a) The causative agent is some bacterium of unknown nature and habitat. This view is obviously similar to that given under 1, (e), but differs in that it does not specify any relation to maize

(b) An infection with some variety of ameba or other protozoon. The frequency of concomitant amebiasis in pellagra has been emphasized by many authors, notably Long in this country. Alessandrini, in Italy, claims to have found a filarial infection of certain wells in pellagrous districts

(c) That the disease is due to a protozoal infection of the blood stream in much the same manner as malaria and trypanosomiasis (sleeping sickness). These views are all based on supposed resemblances in the



epidemiology, endemicity, seasonal occurrence, etc., to these diseases. Some authors have also urged in support of this view the results of treatment. Sambon, who is one of the chief exponents of this view, goes to the length of incriminating some species of *Simulium* (the black-fly, sand-fly or buffalo gnat) as being the agent which carries the organism and by biting the human host injects the protozoa into man. It should be stated that Sambon formulated this hypothesis even to the naming of the carrier as the result of comparative reasoning before entering on his investigations. The hypothesis is attractive and plausible in many respects, but so far lacks much more evidence that simulia are the carriers than the fact that in many places simulia and pellagra are found in the same locality.

This list does not exhaust all the theories which have been propounded but it covers the grounds that have been considered in the work carried out by this Commission.

## II PELLAGRA IN ILLINOIS

Pellagra was first recognized in the State of Illinois at the Cook County institution at Dunning about June, 1909. The diagnosis, first made by Dr. L. J. Pollock, was reported to Dr. W. A. Evans, Health Officer of Chicago, and was confirmed at his request by Passed Asst Surgeon C. H. Lavinder of the Public Health and Marine-Hospital Service in July. Shortly afterwards cases were recognized at the Peoria State Hospital and at the Elgin and Kankakee State hospitals. The diagnosis once made, the managing officers and medical staffs at Dunning and Peoria were able to recall instances of exactly similar eruptions in the past although it was of course impossible to gather any figures which could give any idea as to the actual number of cases. We have therefore thought it advisable to collect only those cases which have been definitely diagnosed since July, 1909. It has been also thought wise to exclude all cases in which there seemed to be any doubt as to diagnosis, although this will probably result in an underestimate of the actual numbers. Another fact which will also tend to render the figures smaller than they should be is that at present the disease is still but little known by the profession at large, and there are undoubtedly cases which are not recognized both inside and outside the state hospitals for the insane. Many attacks are probably of extremely mild character and are not accompanied by any, or but the most transient, constitutional symptoms and are consequently not called to the attention of medical men. It is possible also that errors in diagnosis may have the opposite effect of swelling the totals, as we have seen various skin diseases which have been diagnosed as pellagra, and until the medical profession becomes better acquainted with the characteristic features of the disease it will probably be impossible to get data which are absolutely reliable.

With regard to cases occurring outside the state and county hospitals for the insane, but little reliable information is available. We have been able to collect a few cases, mainly through the kind offices of Dr. George A. Zeller. The State Board of Health has apparently no information on the subject.

The figures for the number of cases in the different institutions, including those at the Cook County institutions at Dunning, have been furnished by the superintendents of each institution with the exception of Peoria, where they are the result of data furnished by Dr. Zeller and the hospital medical staff, by Captains Nichols and Siler and by personal observations at frequent intervals by the members of this Commission. During the height of the pellagra seasons all patients who have previously had attacks of the disease have been examined for evidences of recurrence and on several occasions all patients in the institution have been inspected. Visits have also been made to suspects and others at the Jacksonville, Anna, Watertown and Elgin state hospitals.

Table 1 presents the total number of cases occurring in the three periods, August, 1909, to January, 1910, January, 1910, to January, 1911, and January, 1911, to Sept. 1, 1911, in so far as we have been able to collect them. Recurrent attacks in individuals recorded as pellagrins for the preceding periods are not included a second time, so that the figures represent the actual number of persons attacked.

TABLE 1.—TOTAL NUMBER OF CASES OF PELLAGRA OCCURRING IN ILLINOIS INSTITUTIONS 1909, 1910 AND 1911

	1909		1910		1911		Total			Deaths	Case Mortality
	M	F	M	F	M	F	M	F	Total		
Anna S. H.			3	0	3	0	6	0	6	2	33.3
Elgin S. H.	3	7	2	2	20	4	25	13	38	12	31.6
Jacksonville S. H.	0	0	1	0	0	0	1	0	1	0	0.0
Waukegan S. H.	0	5	0	2	*1	*4	1	11	12	5	41.7
Peoria S. H.	73	104	*42	*25	5	9	120	138	258	128	49.6
Watertown S. H.	0	0	0	*1	0	2	0	3	3	3	100.0
Western S. H.	0	0	0	0	0	0	0	0	0	0	
Lincoln S. S. & C.	0	0	0	0	0	0	0	0	0	0	
Dunning C. I. H.	14	14	18	17	6	7	38	38	76	30	39.5
Cook County Hospital			1	2	5	0	6	2	8	6	75.0
elsewhere			1	1	2	2	3	3	6	3	50.0
Totals	90	130	68	50	42	28	200	208	408	189	46.3

\*One was admitted to the hospital with the disease fully developed. See Table 2.

With the exception of those for Dunning the numbers given in this column include all deaths in pellagrins whether immediately due to pellagra or not.

The figures furnished to the Commission for each year were totals only. It was, however, stated that the sexes were equally affected and hence the figures given for each sex have been estimated by dividing the total by two.

It should be stated that at most of the institutions there have been patients not included in the figures in this table, presenting some suspicious appearances not sufficiently definite in character to justify a positive diagnosis. At Peoria, in 1909, there were a number of such cases and we have a list of forty-nine suspects in 1910. It is probable that some of them were pellagrous, whereas others certainly were not.

In Table 2 is given a list of the cases outside the hospitals for the insane concerning which we have been able to obtain definite information. Dr. Ormsby has kept careful watch on suspected cases at the Cook County Hospital and the diagnosis has been confirmed by him in all those instances recorded in the table. For the sake of completeness there has also been added to this table a list of the cases which have been admitted to the hospitals for the insane with the disease already developed.

TABLE 2—PELLAGRA CASES OCCURRING OUTSIDE THE HOSPITALS FOR THE INSANE

Case	Age	Occupation	Sex	County	Town	Urban or Rural	Hospital	Physician
	30	Housewife	F	Cook	Chicago	C	Cook County	S. Kuh
	58	Switchman	M	Cook	Chicago	C	Cook County	O. S. Ormsby
	44	Porter	M	Cook	Chicago	C	Cook County	O. S. Ormsby
	47	Laborer	M	Cook	Chicago	C	Cook County	W. A. Pusey
	40	R. R. Agent	M	Cook	Chicago	C	Cook County	O. S. Ormsby
	43	Housework	F	Cook	Chicago	C	Cook County	W. A. Pusey
	50	Liveryman	M	Cook	Chicago	C	Cook County	O. S. Ormsby
	42	Upholsterer	M	Cook	Chicago	C	Cook County	S. R. Slaymaker
	37	Housewife	F	Peoria	Peoria	C		J. H. Bacon
	40	Laborer	M	Peoria	Peoria	C		J. H. Bacon
	60		M	Peoria	Peoria	C	Dispensary	J. H. Bacon
	38	Rag picker	F	Peoria	Peoria	C	St. Francis	R. L. Green
	46	Housewife	F	Knov	Galesburg	C		J. H. Bryant
	61		M	Vermilion	Danville			C. E. Wilkins

## Cases admitted to the State Hospitals with the eruption present

C	91	None	M	Henderson	Poor farm		Peoria S H	
P	54	None	M	Woodford	Washburn	R	Peoria S H	
S	42	Baker	F	Mason	Havana	R	Peoria S H	
7	57	Housework	F	Grundy	Mazon	R	Kankakee S H	
S	63	R. R. Foreman	M	Cook	Chicago	C	Kankakee S H	
X			F	Carroll			Watertown S H	

\*C, City, R, Rural or small town, F, Fatal, R, Recovered from this attack

1 Case 6 is recorded in detail in the section on clinical and pathological studies (Case 1, A. D. p. 1) had lived in Mississippi but no attacks had been observed while there.

2 Cases 9 and 10 were sister and brother. Case 9 had seven attacks in seven consecutive years.

3 Case 11 had an attack also in 1910 as well as in 1911.

4 Case 13 had removed to Galesburg from Peoria three months before the onset of symptoms and p. 135.

5 Case 14 lived in West Lebanon, Ind., and went to Danville for medical treatment. He had

008 1909 1910 and 1911.

6 Case D. S., recorded in detail, in full report.

7 Case J. V. recorded in detail, p. 162.

8 This man had had previous attacks in the Panama Canal Zone.

It should further be mentioned that we have heard rumors of cases in Canton, Fulton County, and also in Henderson, Williamson and Rock Island counties

The statistics relating to the Peoria State Hospital will be found in Tables 3, 4, 5 and 6. The first of these shows the average age, the number of cases arising in each decade of life and the relative numbers affected of the two sexes. In Chart 1 is shown a curve representing the month in which attacks have started. The date of onset has often been difficult to fix as it may be extremely insidious and accompanied by but few or no constitutional symptoms. The patients furthermore do not complain of

TABLE 3—ANALYSIS AS TO AGE, ETC

	Average Age*	Decade of Life								Sex		Total
		2nd	3d	4th	5th	6th	7th	8th	9th	Males	Females	
1909	52.3	7	27	40	44	42	14	3	0	73	104	177
1910	57.1	1	9	10	15	20	7	3	2	42	25	67
1911	55.1	0	1	3	5	3	2	0	0	5	9	14
Total	53.7	8	37	53	64	65	23	6	2	120	138	258

\*Youngest 22, oldest 93. Males are to females in the proportion 1:1.15

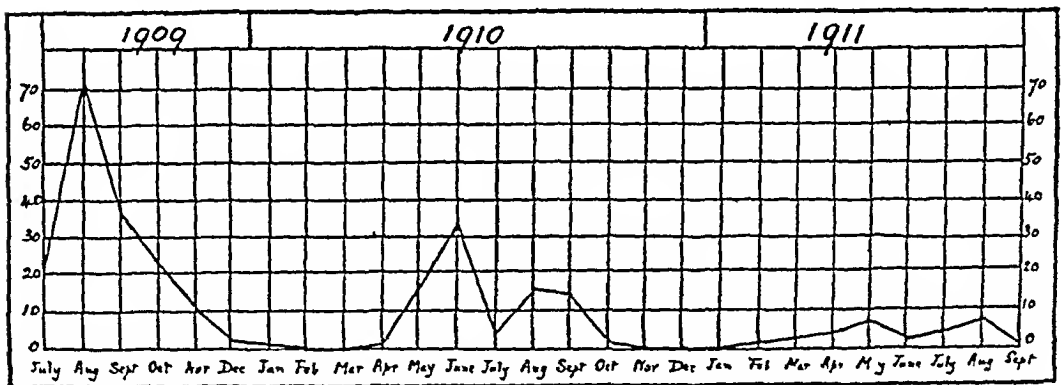


Chart 1—Curve representing the months in which the attacks started

the eruption and often belittle its importance when it is called to their attention. In many cases they are so inaccessible as the result of dementia that direct examination is necessary in order to discover any evidence at all. The figures given in Chart 1 therefore cannot be regarded as entirely accurate, but represent approximately the months in which the disease appears to have become acute. The onset of recurrent attacks has been included in the figures given. It will be observed that one case was noted in January, 1910, and another in February, 1911. Both of these were recurrences in individuals who had had attacks in the preceding year.

In Table 4 are recorded the number of recurrences in patients who have had known previous attacks. Occasionally it is found that patients in whom a positive diagnosis is made are said to have had attacks in previous years, but these have in each instance been recorded as new cases. One of those given as a new case for 1911 is said to have had an attack in the summer of 1910. Furthermore, four of the patients who unquestionably had pellagra in 1909, showed two exacerbations in 1910 which have been recorded, in order to avoid confusion, as only one recurrence for each during that year.

TABLE 4—TABLE OF RECURRENCES

	New Cases	Deaths July, 1909, to May, 1, 1910	Living in Pellagra Season of 1910	Recurrences in 1910	Percentage of Re- currences in 1910	Deaths May 1, 1910, to May 1, 1911	Living in Pellagra Season of 1911	Recurrences in 1911	Percentage of Re- currences in 1911	Deaths May 1, 1911, to Sept 1, 1911	Living on Sept 1 1911
1909	177	97	80	25	31.25	12	68	9	13.24	1	67*
1910	67					11	56	5	8.9	3	53†
1911	14									4	10‡
Total	258						124	14	11.3		130

\*Five of these are now at Kankakee

†Three of these have since died

‡Two of these have since died

In Table 5 is shown the mortality at the Peoria State Hospital. It will be noticed that in a very large percentage death is recorded as being directly due to pellagra. This must certainly be questioned for the year 1909, because at that time there was also an epidemic of amebic dysentery, many of the autopsies showing amebic ulceration of the intestine in the walls of some of which the amebæ were demonstrated by Captains Nichols and Siler. Two cases of liver abscess of typical character were also seen. It has seemed impossible in many cases to determine what weight is to be assigned to pellagra as the primary cause of death and how much belongs to any other coexisting disease. It has therefore seemed advisable to make no subdivision which could only be misleading. In those cases recorded as dying from some other cause there were no active pellagrous symptoms present at the time of, or shortly before, death.

In discussing these tables attention may first be directed to the class of individuals most affected. In general it may be said that the disease is especially frequent for some reason at present unknown among the chronic insane. Most of the patients who have suffered from pellagra have belonged to the groups of defectives, senile dementes, epileptics, and

the terminal stages of dementia præcox. They have been for the most part poorly nourished and in an enfeebled state of bodily health. The total population of the Peoria State Hospital during the great epidemic of 1909 was about 2,100, and of this number of patients we find at least 84 per cent showed definite symptoms of pellagra. Yet during this period none of the employees suffered from the disease in spite of the fact that they were exposed fully as much to the bites of insects and drew their food and water supply from exactly the same source as the patients. This freedom from pellagra on the part of physicians, nurses, attendants and other employees has been absolute in all the institutions. It is, furthermore, almost certain that some of these employees have been in a run-down state of health at some time during the seasons in which pellagra was rampant.

TABLE 5 —MORTALITY AT THE PEORIA STATE HOSPITAL

	Pellagra Given as Immediate Cause		Other Causes		Total Deaths	Percentage of Cases
	Number	Per cent	Number	Per cent		
1909	89	81.0	21	19.0	110	62.15
1910	8	63.7	6	36.3	14	16.42
1911	4	100.0	0	0.0	4	28.57
Total	101	78.9	27	21.1	128	49.61

## OTHER CAUSES OF DEATH

Pulmonary tuberculosis	6
Valvular heart disease	4
Pneumonia	4
Epilepsy	2
Cerebral hemorrhage	2
Cerebral embolism	1
Cholecystitis	2
Amebic dysentery	1
Chronic nephritis	1
Senile gangrene	1
General paralysis of the insane	1
Carcinoma uteri	1
Accidental	1
	<hr/> 27

While the general statement made above is true that the individuals have been weakly and ill-nourished there are, however, notable exceptions. Some of the pellagrins have been apparently robust and well nourished. In this connection it may be of interest to refer to a patient seen by Dr. Oliver S. Oimsby in 1911 who does not figure in the tables given here, as the disease was contracted in Kentucky and the patient came to Chicago only for medical advice. This lady was 44 years of age, native of Maine, but had lived in Kentucky for twelve years where she was at

the head of a college department of domestic science Her duties, therefore, consisted of the teaching of hygiene as regards management and dietary of the household She had had attacks of "morning diarrhea" for several summers and was subject to attacks of acute indigestion The first known attack of dermatitis occurred in October, 1910, but was very mild and without severe constitutional symptoms The second attack, in 1911, was much more severe and led her to come to Chicago for assistance When seen she presented an entirely characteristic skin eruption of pellagra involving the hands, arms, forearms and across the sternum, with sore mouth and diarrhea In spite of this she appeared to be in a good state of nutrition With such facts before us it is certainly difficult to understand the freedom of hospital employees

Attention should be directed to the coexistence of intestinal parasitism with the larger outbreaks of pellagra at the Peoria State Hospital, 1909 also saw an epidemic of amebic dysentery and we find that since that year pellagra has subsided very rapidly It is of course possible that the enormous fatality during 1909 may have removed most of the more susceptible individuals The question of the relation of protozoal infection to pellagra is more fully discussed in later sections of this report

The dietary of the state hospitals is also the subject of detailed study later It may, however, be mentioned here that the most notable point in the dietaries has been a deficiency of animal protein, and yet the institution feeding the smallest amount of meat, which forms the main source of this material, has shown no pellagra

A few words are available in regard to the habits of the patients which would expose them to biting by insects, etc In all institutions patients are out of doors as much as possible At Peoria probably the majority of the patients who have contracted pellagra have spent the time while out of doors, sitting on the porches of the buildings which they leave only for a short time if at all So many have been more or less helpless demented that any more active outdoor life has been out of the question Others it is true have had the free run of the grounds It should be noted that this outdoor period of the day does not include the early morning and late evening, at which time blood-sucking insects would be most prevalent Furthermore, many attacks of pellagra have arisen in patients confined to the hospital wards, who were not out of doors at all

In this connection reference may be made to the striking example quoted by Dr Hyde<sup>1</sup> from the Elgin State Hospital The patient a woman, had been bedridden for years and occupied a room in common with another insane woman, also pellagrous The first patient occupied a bed at the farther extreme corner of an apartment lighted by a single window The only light accessible for a long period prior to the advent

of the pellagrous disorder was furnished by this one window. It is but fair to state that inquiries at the Elgin State Hospital failed to elicit the name of this patient, but the medical staff has changed since this observation was made (1909). The facts are substantiated, however, by Dr. Ormsby, who was with Dr. Hyde on the occasion of the visit.

With regard to insects such as fleas, bed-bugs and body-lice, it cannot be said that any institution is entirely free from them, but they certainly are not numerous in any of the hospitals where constant warfare is maintained against them.

The distribution of the cases in the different wards and buildings at the Peoria State Hospital, built strictly on the cottage plan, revealed no special foci. Cases apparently originated in all of them and were not more common even in those cottages in which a large number were segregated for observation. Furthermore, there were no differences in the dietary of the different wards with the exception of the hospital wards, all being supplied from the same kitchen.

#### DISTRIBUTION

As regards the distribution of pellagra throughout the state outside the hospitals for the insane, we feel that the data are still too few to justify any conclusions. It is certainly striking that the great majority of the cases on which we have definite information have arisen in persons living and working in the two largest cities in the state, Chicago and Peoria. This is contrary to general experience in Italy and elsewhere. Sambon states that pellagra does not occur in big cities and bases much of his reasoning as to the relation with simulia on this point. He claims that simulia do not enter large cities or human habitations. In this respect he is certainly wrong as regards some species, e. g., *S. venustum*. Sambon believes the disease to be almost confined to agricultural laborers and explains the few instances in which city dwellers have been affected by occasional visits to the country. Such reasoning is difficult to refute as most people occasionally go beyond the city limits. There seems to be one possible explanation for the difference in the experience in this state as compared with that in Italy. The disease has only recently been recognized here and it is obvious that the country practitioner is likely to be the last to become informed concerning it. Nevertheless there has been so much written in the lay, as well as the medical press concerning the disease that it seems hardly possible that the majority of the doctors throughout the country districts have not become acquainted with its prevalence and very striking and obvious characteristics. A further fact is also pertinent on this point. If, as is claimed by those most competent to judge, pellagra leads sooner or later to manifestations of mental disorder, surely the state hospitals would be receiving more examples



Judging from the experience of Sambon in Italy, if the disease were so much more common in agricultural communities than in large cities, there should be several hundred pellagrins in the country districts to balance the few we have been able to collect in Chicago and Peoria among persons who are strictly city dwellers. This point can only be determined by a careful investigation of the rural population of the state, and seems to us a very proper subject for investigation by the State Board of Health.

Until such investigations are made it would be unwise to attempt to state the probable number of pellagrins at present in the state of Illinois. Our tables show that there has been a marked decrease in the number of fresh cases at the Peoria State Hospital, whereas at Elgin they have increased. But another fact which must be regarded as disquieting is that the numbers outside the state hospitals, while still very small, are increasing. It seems to us advisable that every effort should be made to determine the actual numbers at the earliest possible date in order to be able adequately to determine the progress which the disease is making. As a conservative estimate we would say that since July, 1909, when the disease was first recognized, there have been 500 cases in this state.

### III CLINICAL AND PATHOLOGICAL

It has not been thought necessary to include in this report a detailed description of the various manifestations of pellagra, since many excellent articles covering this ground have already been published by various authors.<sup>1</sup> We propose to give only the results of our own observations, with brief descriptions of the main characteristics. With regard to pathological material we have been at a disadvantage in that it has been difficult to obtain necropsies on undoubted cases until within the past few months. The microscopical examination of the nervous system is consequently yet far from complete. The cases on which the pathological examinations were made are reported in some detail below and have been obtained from the following sources:

Case 1 was studied by the courtesy of Dr W. A. Pusey at the Cook County Hospital, Case 2 from the Kankakee State Hospital, Cases 3, 4, 5 and 6 from the Elgin State Hospital, the autopsies with the exception of three being performed by the medical officers of that institution. Cases 7 and 8 were from the Peoria State Hospital, the autopsy in Case 7 having been performed by Dr Ellis of that institution.

The clinical study has been made on six cases transferred from the Peoria to the Kankakee State Hospital on cases arising in the latter hospital, together with material collected on frequent visits to Peoria.

*Cutaneous System*—In a study of more than two hundred patients, the manifestations exhibited on the skin were sufficiently characteristic

to enable one to make a diagnosis of the general condition. In general, the symptoms corresponded to the cases described abroad, in Italy and other countries. It can hardly be said, however, that they were exhibited in the stages which have artificially been made in European cases. Rather than being stages of disorder they appeared to exhibit degrees of activity of the process. The arrangement of the lesions was characteristic.

In the major portion of the cases the dorsum of the hands, the wrists and some parts of the face, neck or scalp were involved. The disease only occasionally involved the feet or ankles, areas which were so often affected in the European cases. In a large number, the lesions occurred on the arms and chest, in a smaller percentage, the ears and other parts of the body were involved. In a very few, the inflammatory process involved the palmar surface of the hands, and occasionally the eruption was generalized. The peculiar collar described abroad, while seen here occasionally, was not common. In the case of several women, quite a severe dermatitis occurred about the vulva and involved the mucous membrane of the vagina. The lesions were always symmetrically placed and ran through a pretty typical course. In the major portion, the distribution on the hands was as follows: a solid area extending over practically the entire dorsal surface of the hand, involving the fingers to the knuckles, also the wrist on the extensor surface for a distance of about two inches. In the latter area it would frequently sweep around and involve about two-thirds of the flexor surface then come to an abrupt ending. This particular gauntlet was interesting and occurred frequently.

In the most moderate degree of erythema, the process went through about the following course. Large macular lesions, light or dark red would appear, which soon fused, forming a patch of dermatitis almost identical in appearance with that caused by the sun. After a period of from seven to fourteen days or a little longer, desquamation would begin, at which time a roughened scaling surface was presented. Early in the process, moderate to marked swelling was usually present. No subjective sensations were complained of. That none was present was manifest by the absence of any signs of interference on the part of the patient. In some patients, pigmentation occurred while in others after desquamation was complete, the area was lighter than formerly. In the more active cases, on the erythematous base bullous lesions would soon develop. Some of these were very large. After several days they would gradually dry, leaving a thickened, crusted epidermis. Secondary pyogenic infection not infrequently followed in the vesicular and bullous cases. In many the edema was sufficient to produce fissures to quite a marked extent. The lesions, whether erythematous or bullous, were

always well defined. It was particularly noticeable that after the bullous lesions had cleared the skin was somewhat thinner than formerly and there was no hyperpigmentation. In the older patients, where the process was subacute, the areas presented the appearance of a simple chronic dermatitis with marked hyperpigmentation. The atrophy described in chronic cases in Europe was present to a slight degree only. Loss of pigmentation did occur, but true cutaneous atrophy has been uncommon. That sunlight played a part in producing or determining the location of lesions was demonstrated by having suspected patients wear fenestrated gloves, when the eruption would be largely limited to the exposed surfaces. We have, however, seen many patients exhibiting typical lesions occupying the hands and other usual areas who were not exposed to the direct rays of the sun at any time. Bedridden patients developed lesions in the same situation as those able to be out of doors. That the cutaneous lesions resemble an ordinary sunburn was frequently emphasized by reports of attendants stating that certain patients were suffering from sunburn, which on examination proved to be a pellagrous erythema. The importance of the cutaneous symptoms is at present paramount, for without them a diagnosis can rarely be made. It is probably true that the disease may occur without these symptoms, but in the present state of knowledge they are essential in arriving at correct conclusions.

*Pathology*—Cutaneous. In a large number of sections studied, the general picture was that of an angio-neurotic process, and resembled to a marked extent that seen in multiform erythema. The most marked change was noticed in the superficial part of the corium, almost all infiltration occurring in the pars papillaris. The specific findings are as follows. With a low power, the stratum corneum was thickened, the stratum granulosum and rete practically normal. The upper portion of the corium showed inflammatory reaction, and the connective tissue appeared edematous. With a high power the hyperkeratosis was seen to be well marked. Here and there, areas of parakeratosis were present, as evidenced by the presence of nuclei extending to the upper layer of the stratum corneum. Many pigment granules were present. The rete was practically normal, except in places where its integrity was interfered with by infiltrating cells. In the papillary layer cellular infiltration was quite marked, particularly in the region of blood vessels. Collagen and elastin were present, the former showing edematous changes. The deeper parts of the corium were comparatively normal. In parts of the papillary layer elastin was absent.

From a survey of these findings, no specific statement can be made concerning the process. No microorganisms were found. That the process was moderately destructive, was evidenced by the absence of certain structures. As a whole, there appeared to be a reaction on the

part of the skin either to a local toxic irritant or an angio-neurotic process influenced from a distant focus

*Gastro-Intestinal System*—The symptoms referable to this system unquestionably stand next in importance to the skin lesions and are present in a very large proportion of all cases. They seem to be especially marked in all more severe examples. They cannot, however, be regarded as characteristic inasmuch as very similar manifestations are also met with in other disorders. We would hesitate to base a diagnosis upon them in the absence of typical skin lesions.

The tongue becomes swelled and denuded, presenting a bright red appearance with, in severe cases, more or less ulceration along its edges and on its under surface and the appearance of yellowish sloughs in these regions which bleed very easily. The lips and cheeks, where they come in contact with the teeth, also show, in the more serious forms, a similar bleeding, sloughy appearance. The whole condition presents features which are very similar to the aphthous stomatitis seen in other debilitating states, especially in children, but also in adults, as, for example, in pemphigus. The ulcers are always superficial and in the event of recovery heal without leaving scars. This state of the mouth is often very painful and renders eating difficult. In the slighter forms there is usually nothing more to be seen than a redness and smoothness of areas, especially at the tip and along the margins which has received from Sandwith the name of "bald-tongue." Scrapings from the sloughing surface have not shown the presence of any mycelial growth.

Diarrhea has also been a very constant concomitant, being as a rule more severe in those cases which terminate fatally. In the milder cases close questioning may be necessary to find that there has been a looseness and excessive action of the bowels and we have in some been able to obtain no such evidence. In this regard some attention must be paid to the class of patient with whom, in the main, we have had to deal, a class of chronic demented from whom but little information can be obtained directly. Nevertheless, it has appeared that in some there has been either no change in the usual state of the bowels, or there has been even constipation. The appetite may be preserved and in some cases it has even appeared to be excessive, especially in relation to the actual digestive capacity. In more severe cases, however, appetite is poor.

*Mental and Nervous System*—The classical descriptions of pellagra give somewhat vague accounts of the symptoms due to involvement of the nervous system, especially in regard to the mental picture. The material at our disposal is unfortunately almost entirely unsuited for a study of this question, since almost all cases have arisen in patients already suffering from mental disorder and presenting more or less evidence of interference with the projection system. In most instances

the records of previous examination of the nervous system are almost entirely lacking and it is hence impossible to decide which, if any, of the present manifestations are due to pellagra. In Cases 1 and 2 recorded below, and another seen with Dr. Baker of Peoria, where pellagra occurred in individuals previously healthy, there were no evidences of gross lesion of the nervous system except in the final stages. The exaggeration of reflex did not appear to be more than could be accounted for by the condition of exhaustion. In the final stages there have in many cases developed symptoms of central neuritis, and this must unquestionably be regarded as worthy of more than passing mention. It will be discussed further in considering the course of the disease.

With regard to mental symptoms, we can quote but two cases which bear on the point. In the first of these there developed a psychosis of delirious character which appeared to run parallel to the physical manifestations. Besides this, there was an intensification of the querulousness peculiar to the personality of the patient together with some depression and irritability. In the second case a typical manic-depressive excitement arose shortly after the appearance of gastro-intestinal symptoms which seems to have been the early manifestations of an attack of pellagra. The scanty history of this individual prior to the onset which was available, seemed to indicate that she had had periods of depression with mutism and apathy, which would suggest the occurrence of transient depressed phases of manic-depressive insanity. Hence one is not justified in regarding the manic excitement as a picture forming part of the pellagra complex. It is to be considered only as a personal type of reaction.

In Case 1, quoted below, the patient showed no mental symptoms up to the time of her death beyond a change in disposition in which she became more depressed and irritable. This may be considered as probably adequate to her general condition of weakness and exhaustion. Another case of interest in this connection is that seen by the courtesy of Dr. J. H. Bacon<sup>2</sup> in the city of Peoria. In a personal communication Dr. Baker informs us that this patient, who had seven attacks of pellagra in seven consecutive years had become more irritable and depressed ever since the first attack in 1903, but there were no more definite mental symptoms until the last and fatal attack in 1910. The depression then became more marked although still accompanied by insight. During the last stages she also had episodic periods of apprehensive excitement accompanied by sense falsifications and extreme restlessness. These episodes occurred mostly at night and were followed by amnesia. During them she threatened suicide, accused her daughter of immorality and

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<sup>2</sup> Bacon, J. H. A Case of Pellagra in Illinois. Jour. Am. Med. Assn. May 28, 1910, p. 1783.

heard robbers trying to break into the house. During the intervals she was depressed and hopeless but was able largely to direct the affairs of her household from her bed.

Among individuals already insane there have been no definite changes produced by the onset of pellagra. Some are reported as having been more restless and excited, others have seemed more depressed and irritable but in the vast majority the pellagra does not seem to have led to any change in the mental attitude of the patient.

From our personal experience we therefore do not feel justified in making any very definite statements regarding the nervous and mental symptoms of pellagra. It has seemed that in the projection system there are no characteristic changes until the final stages when there is a great liability to the occurrence of central neuritis. (In this relation the observation of increased sensitiveness of nerve trunks and muscles to pressure, made in Case 2 at the time of a generalized pellagrous eruption, is of considerable interest in that it suggests that the nerve trunks are susceptible to the pellagrous toxin whatever be its nature.) In regard to the associative system of the brain, our observations would suggest that there is a liability to the occurrence of deliria similar to those seen in other infective and toxic states. Here reference may be made to the report of the Georgia State Sanitarium at Milledgeville for 1910. A large number of patients were admitted to this institution suffering from pellagra with mental symptoms and it is interesting to note that the psychoses presented are included in the infective-exhaustive group which contains the deliria due to bacterial and other organic toxins. Apart from this acute condition, which is to be regarded only as a type of reaction on the part of the brain to acute intoxication of any kind, there does not seem, in our limited experience, to be any "pellagrous insanity." The change in disposition, which is not by any means constant, is very similar to that seen in other chronic exhausting diseases such as tabes dorsalis and tuberculosis.

In our opinion it still remains to be proved that pellagra gives rise to any more chronic form of nervous or mental disorder. It does give rise to symptoms of acute intoxication of the nervous system such symptoms being not in any way characteristic of any particular toxin. Furthermore, like other intoxications, it may act as the exciting cause for the outbreak of acute psychoses, such for instance as those belonging to the manic-depressive group, in individuals who are susceptible.

There is one further point which is also especially worthy of emphasis although its explanation is still to be found. This is the great susceptibility of the chronic insane to pellagra. The proportion of those affected outside the state and county hospitals for the insane to the inmates of these institutions is certainly extremely small in this state even if allowance be made for many failures to recognize the disease.

## INTESTINAL BACTERIA AND PROTOZOA

1 *Bacteria*—A very extensive study of the intestinal bacteria has been carried out, the results of which will be merely summarized here

Altogether twenty-two stools from fourteen patients were examined as well as two samples taken from the intestinal canal post mortem in one of these fourteen cases. Of the first ten specimens, three, Nos 5, 8 and 7, were furnished by inmates of the Kankakee State Hospital who showed a suspicious pigmentation of the skin, but in all probability did not have pellagra, five, Nos 2, 3, 4, 6 and 9, were from pellagrins well on the road to recovery from an attack of the disease, which has not recurred in them up to the present time, August, 1911, two specimens, Nos 1 and 10, were from pellagrins who had recently suffered a very severe acute attack and in whom the skin lesions had practically disappeared, although the patients still remained very weak and apparently about to die. The other fourteen specimens seemed to be, as a whole, more nearly representative of the condition of the stools in pellagra. Six of them, Nos 11, 12, 14, 16, 18 and 20, were obtained at intervals from the same patient, W N, and during this time the skin lesions evolved in such a way as to indicate an acute exacerbation of the disease, and the erythema appeared on a new area, the forehead, gradually extending downward over it, and finally, before the last specimen was obtained, the patient had recovered. Two specimens, Nos 15 and 21, were obtained from another patient, the first one during a recurrence of the skin eruption, and the second after all skin manifestations had disappeared. One specimen, No 13, was obtained from a patient in whom the skin lesion had persisted for months, indicating a chronic type of the disease. Two others, Nos 17 and 19, were obtained from patients soon after the recognition of a recurrence of the skin eruption. Finally, the last three specimens were obtained from a fatal case in which the eruption had been present for three months, and was very severe at the time. One specimen, No 22, was a fluid stool obtained forty-one hours before the death of the patient, and the second, No 23, was obtained from the cecum, and the third, No 24, from the ileum at the autopsy, twenty-one hours after the death of the patient.

In the complete report, the observations have been recorded in detail. These included the numerical and differential counts of the bacterial cells in the feces, quantitative plate cultures of the mixed fecal flora on aerobic litmus-lactose-agar, aerobic litmus-lactose-gelatin, aerobic blood-agar, anaerobic litmus-glucose-agar and anaerobic blood-agar, Veillon-tube separation cultures in glucose-agar, plate cultures of the bacterial spores of the feces on aerobic litmus-lactose-agar, anaerobic glucose-agar and anaerobic blood-agar, fermentation-tube cultures of the mixed fecal flora in dextrose-broth, levulose-broth, lactose-broth and

Among these 100 strains only a few manifested any distinctly different behavior toward the sera of pellagrins as compared with the sera of normal individuals. These were Strains 14, 35, 44, 62 and 67 and possibly 85 and 88.

Following is a brief description of the characteristics of the five strains, 14, 35, 44, 62 and 67.

Strain 14 was derived from a thin colony, spreading beneath the surface, on an aerobic blood-agar plate inoculated with unheated suspension of Specimen 11. This specimen was a watery stool passed by the patient W. N. early in an exacerbation of definite pellagra. The culture was found to be impure and was separated into two strains by plating during January, 1911. The strain then designated as 14B gave the more definite agglutination reactions and was accepted as the authentic Strain 14, the other component being disregarded. The organism was an actively motile bacillus, varying in thickness from 1.0 micron to 1.8 microns and in length from 2.1 microns to 8.1 microns. The ends were rounded. In gelatin stab culture it produced a funnel-shaped liquefaction. In litmus-milk the reaction remained alkaline, the milk was slightly curdled after four days and the curd dissolved to some extent afterward. No gas was produced in broth containing dextrose, levulose, lactose, maltose or saccharose. There was no production of indol in Dunham's peptone-salt solution. On agar slants the growth was white at first but later became orange in color.

The contaminating organism separated from the above strain by plating the original Strain 14, was designated as Strain 14A. In its various characters it agreed closely with *B. coli*.

Strain 35 was derived from a colony on the aerobic blood-agar plates inoculated with unheated suspension of Specimen 14. This stool was passed by a pellagrin showing active erythema on the hands, but the usual precautions against the contamination of the stool were not carried out. The organism was an actively motile bacillus of about the same size as *B. coli*. In gelatin stab culture it produced a funnel-shaped liquefaction. In litmus-milk the reaction remained alkaline but there was slight coagulation after four days. No gas was produced in broth containing dextrose, levulose, lactose, maltose or saccharose, and indol was not produced in Dunham's peptone-salt solution. Pigment was not observed in the culture of this strain, so that it differed from Strain 14 in this respect.

Strain 44 was derived from a colony on the aerobic plates of litmus-lactose-agar inoculated with unheated suspension of Specimen 17. This stool was passed by a pellagrin showing a subacute, active erythema on the hands. The organism was an actively motile bacillus resembling *B. coli* in size and shape. In gelatin stab culture there was no lique-



faction, but gas bubbles were seen in the gelatin after three days. Litmus-milk was rendered acid in twenty-four hours and coagulated in forty-eight hours. No subsequent digestion of the clot was observed. Gas was produced in fermentation-tube cultures in broth containing various sugars as follows: Dextrose, 95 per cent gas in the closed arm; levulose, 45 per cent; lactose, 40 per cent; maltose, 62 per cent; saccharose, none. Cultures in Dunham's peptone-salt solution gave a pronounced positive reaction to the test for indol. Pigment was not observed in the cultures of this strain.

Strain 62 was derived from a colony on the anaerobic plates of glucose-agar inoculated with unheated suspension of Specimen 19. This stool was passed by a pellagrin with definite active pellagrous erythema on the hands, which had been noted first about three weeks before. The organism was a granular bacillus appearing somewhat larger than *B. coli*, some of the rods being very long. Most of the colonies on the set of glucose-agar plates were composed of similar bacilli. In gelatin stab culture there was no liquefaction, and gas bubbles were observed after eleven days. Litmus-milk was acidified in twenty-four hours and coagulated in forty-eight hours. There was no subsequent digestion of the casein. In fermentation-tube cultures in broth containing various sugars, gas was produced as follows: Dextrose, 45 per cent; levulose, 45 per cent; lactose, 45 per cent; maltose, 50 per cent; saccharose, none. Indol was produced in Dunham's peptone-salt solution. A slightly red pigment was observed in some of the cultures of this bacillus.

Strain 67 was derived from a colony on the aerobic blood-agar plates inoculated with unheated suspension of the same Specimen 19. The organism was an actively motile bacillus with rounded ends, about 4 microns long by 1.4 microns thick on the average. Variations in length between 2.4 and 6.2 microns and in thickness between 1.0 and 1.6 microns were observed. The flagella were peritrichous and apparently numbered from four to ten for each cell (this point was not satisfactorily ascertained). In gelatin stab cultures, it produced a funnel-shaped liquefaction resembling closely that produced by Strain 14 and Strain 35. In litmus-milk the reaction remained alkaline but there was slight coagulation after four days and some digestion of the casein apparent at this time but more definite subsequently. No gas was produced in fermentation-tube cultures of broth containing dextrose, levulose, lactose, maltose or saccharose. No indol could be detected in cultures grown in Dunham's peptone-salt solution. Fresh agar cultures were colorless, but later became orange in color. This strain corresponded in its various characters very closely to Strain 14 and, except for the pigment, it also agreed well with Strain 35.

TABLE 9—SUMMARY OF RESULTS OF AGGLUTINATION TESTS PREVIOUS TO JULY, 1911

	Positive Results					Negative Results				
	Strains					Strains				
	14	35	44	62	67	14	35	44	62	67
SERA OF NORMAL INDIVIDUALS										
Kerr .	0	0	0	0	0	4	1	3	3	3
MacNeal	0	0	1	1	0	5	1	2	2	5
Guinea-pig	0	1	0	0	0	2	0	2	3	3
<i>Total</i>	0	1	1	1	0	11	2	7	8	11
SERA OF INSANE PATIENTS, NOT PELLAGRINS										
M L	1				2	0				0
B N	1				2	0				0
<i>Total</i>	2				4	0				0
SERA OF PELLAGRINS										
P E	2	1	2	1	2	1	0	0	1	0
M Y	1	1	1			1	0	0		
M G	4	1	2	2	4	0	0	0	0	0
G I	1	1				1	0			
T E	1	1	0	0	4	3	0	2	2	0
D E	1		1	2	1	0		1	0	1
W N	1		1	2	2	0		0	0	0
J S	1		0	0	0	0		1	1	1
E P	1		0	1	0	0		1	0	1
D D	1		0	0	1	0		1	1	0
A D	2		0	0	2	0		1	1	1
S E	1				2	0				0
J N	1				2	0				0
<i>Total</i>	18	5	7	8	20	6	0	7	6	4

In Table 9 are given in summary the results of agglutination tests on these five bacterial strains with the sera of pellagrins and various controls which were made prior to July, 1911, and the total number of positive and negative tests on the different classes of sera are seen to be as follows

	Strain 14		Strain 35		Strain 44		Strain 62		Strain 67	
	+	—	+	—	+	—	+	—	+	—
Normal Controls	0	11	1	2	1	7	1	8	0	11
Insane Controls	2	0							1	0
Pellagrins	18	6	5	0	7	7	8	6	20	1

TABLE 10—SUMMARY OF RESULTS OF AGGLUTINATION TESTS ON STRAIN 67  
DURING JULY AND AUGUST, 1911

## SERA OF HEALTHY INDIVIDUALS

Individual	Residence	Remark	Posi- tive Results	Nega- tive Results
MacNeal	Urbana		0	16 <sup>1</sup>
York	Urbana		15	0
H E	Urbana		3	0
H D	Chicago		0	3
M Y (C)	Chicago		0	2 <sup>2</sup>
M Y (K)	Kankakee		1	0
Monkey 248	Kankakee		0	1 <sup>2</sup>
Monkey 290	Kankakee		0	1 <sup>2</sup>
Total			19	23

## SERUM OF MONKEY FED ON CULTURES OF STRAIN 67

Monkey 79	Kankakee		2	0
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## SERA OF PATIENTS NOT PELLAGRINS

B R	Kankakee	Insane	0	1
M R	Kankakee	Insane	0	1
W L	Kankakee	Insane	1	0
P N	Kankakee	Insane	1	0
W D	Kankakee	Insane	0	1 <sup>2</sup>
P L	Kankakee	Insane	1	0
J S	Kankakee	Insane	1	0
A A	Chicago	Sane, syphilis	0	1
R Y	Chicago	Sane, syphilis	0	1
B I	Chicago	Sane, syphilis	1	0
L S	Chicago	Sane, syphilis	0	1
C K	Chicago	Sane, syphilis	0	1
O Y	Chicago	Sane, typhoid	1	0
G I	Chicago	Sane, pneumonia	2	0
Total			8	7

## SERA OF PELLAGRINS

A D	Chicago	Sane	4	0
C C H	Chicago	Sane	3	0
D Y	Chicago	Sane	9	0
G M	Chicago	Sane	2	3 <sup>3</sup>
T R	Chicago	Sane	3	0
G S	Chicago	Sane	3	1
M G	Peoria	Insane	1	0
D E	Peoria	Insane	0	2
S N	Peoria	Insane	5	0
P Y	Peoria	Insane	1	0
B N	Peoria	Insane	3	0
C N	Peoria	Insane	6	0
B R	Kankakee	Insane	0	2 <sup>2</sup>
S E	Kankakee	Insane <sup>4</sup>	0	2
M N	Kankakee	Insane	6	0
Total			46	10

1 Four of these were slight agglutinations

2 All of these were slight agglutinations

3 Two of these were slight agglutinations

4 Diagnosis of pellagra doubtful

These tests directed attention particularly to Strains 14, 35 and 67, and especially to the last one

In Table 10 is a similar summary of the results of the agglutination tests on Strain 67 with various sera, performed during July and August, 1911

These results tend to break down the evidence suggesting that these bacterial strains bear a special relation to the disease pellagra, by showing that positive agglutination of them is frequently brought about by the sera of normal individuals and that the sera of pellagrins sometimes fail to produce this result. Some of these results, however, did support, in a way, the earlier evidence, especially the positive agglutinations of Strain 67 produced by the serum of every one of the acute typical cases of pellagra in sane individuals in the Cook County Hospital

In the complete report the observations are set down in detail without any attempt to discuss the data. It is quite evident from a consideration of them that further experimental work is necessary before it will be possible to draw any important conclusions concerning questions in this field. The following conclusions are, at any rate, suggested by the observations and may be set down here in a tentative way

1 In pellagra, especially in the acute attack, there are marked changes in the fecal flora as compared with the normal. Relative diminution in the number of bacterial cells per milligram of feces is frequently very great. The numerical relations of the different types of bacteria normally seen in the feces are disturbed, and in addition several new forms, more or less heterogeneous in nature, appear. Protozoa, amebae and flagellates are frequently present

2 In cultures from the feces of pellagrins, various departures from normal relationships of the fecal bacteria are frequent, and many forms of bacteria occur which are not found in cultures of fecal bacteria of healthy men

3 Three bacterial strains derived from three different cases reacted to agglutination tests with sera of pellagrins in a manner somewhat suggestive. These strains, 14, 35 and 67, were all derived from pellagrins at Peoria, but they were agglutinated by sera of pellagrins at Kankakee and at Chicago as well as sera of patients at Peoria. This somewhat suggestive evidence of a relationship to pellagra is refuted or very much weakened by the fact that these bacteria were also agglutinated by the sera of insane persons free from pellagra at Peoria and at Kankakee, and by the sera of apparently normal persons at Kankakee, at Chicago and at Urbana. Preliminary cultural investigation has suggested that two of these strains (14 and 67) are probably identical in nature, and that perhaps the other strain (35) is a closely related variety of the same species. They do not belong in the *B. coli* group

4 Other bacterial strains which showed suggestive agglutination relations were all non-h liquefying, gas-forming bacteria, probably closely related to *B coli*

## 2 Protozoa

### PEORIA

#### 1 Protozoal infection among fifty non-pellagious patients

Number showing entamebas (26), 52 per cent

Number showing flagellates (30), 60 per cent

Of these fifty patients, eleven presented a definite and clear-cut clinical picture of amebic dysentery. Entamebas were demonstrated in 73 per cent of these cases giving clinical evidence of dysentery, and in one case an amebic abscess of the liver was found at necropsy.

#### 2 Protozoal infection among twenty-one pellagious patients

Number showing entamebas (16), 76 per cent

Number showing flagellates (16), 76 per cent

A further analysis of these statistics and comparison with clinical symptoms exhibited by each patient demonstrated the fact that of the twenty-one pellagious patients five were suffering with dysentery resembling in all respects amebic dysentery. Entamebas were present in all five cases. Of the remaining sixteen cases, six presented diarrheic symptoms, and in five of the cases suffering from diarrhea entamebas were present. The remaining ten cases gave no evidence of either diarrhea or dysentery, but in six of these cases entamebas were present in the stools.

An attempt was made to classify the species of entamebas found in the patients at Peoria. The examination of fresh preparations was the routine method for all cases, but in many instances staining methods were used. The staining methods adopted were the following polychrome stains (Leishman's, Wright's, MacNeal's, and Giemsa's) and the iron hematoxylin method of Heidenhain. It was possible definitely to establish the fact that at least three and probably four species of entamebas were present.

*Entamoeba histolytica* was found in four cases.

*Entamoeba coli* was present in a number of cases.

*Entamoeba tetragena*. An entameba resembling in all respects the published descriptions of *E tetragena* was found in some cases.

A number of preparations stained with polychrome stains and iron hematoxylin, and material containing encysted entamebas, were forwarded to Captain C F Craig, Medical Corps, U S A, for an expression of opinion. Captain Craig reported finding *E coli*, *E histolytica* and *E tetragena*, thus confirming the findings of Captains Siler and Nichols.

It is quite evident that the most common form of dysentery at the Peoria State Hospital was due to amebas, for the following reasons. The typical clinical symptoms of amebic infection were present, pathogenic entamebas were present in the stools, and in many of the cases going to autopsy amebic ulceration or folliculitis was noted.

The flagellates found at Peoria were mainly *Trichomonas intestinalis*.

A statistical study of protozoal infection of the intestinal canal was undertaken among the patients (practically all non-pellagrous) at Kankakee and Dunning, without reference to the presence or absence of diarrhea or dysentery. The following results were obtained.

#### KANKAKEE

##### Examination of sixty-two patients

Number showing entamebas (36), 56 per cent

Number showing flagellates (48), 77 per cent

No attempt was made to classify the types of entamebas encountered. The flagellates were, in the large majority of cases, *Trichomonas intestinalis*.

#### DUNNING

##### Examination of fifty patients

Number showing entamebas, 46 per cent

Number showing flagellates, 32 per cent

At this institution, also, our time was limited and no attempt was made to classify the types of entamebas. In most instances, the organisms were "resting" or encysted. The flagellates were *Trichomonas intestinalis*.

The presence of entamebas and other protozoa, pointed out by Nichols and Siler in 1909, has since been exploited by several writers, notably Long, who carries his views to the extreme of considering pellagra a complication of amebic dysentery. We could find no support for such a view in our results at Peoria.

Careful stool examinations were also made of the patients occupying two cottages in which experimental corn and corn-free diets were instituted and carried out for a period of one year. A summary of the results of these examinations is as follows.

	Number of Patients	Cases Showing Amebas	Cases of Pellagra Showing Amebas	Cases of Pellagra Without Amebas
Corn diet	59	7	1	3
Corn free diet	58	6	0	5

To add light relative to the extent of protozoal infection in the state hospital at Kankakee, Dr J T Rooks examined a group of patients on admission and again at a later date This study was made for the purpose of determining whether the infection took place after admission, and whether or not these organisms were pathogenic Only a summary of Dr Rooks' work is here appended

TABLE 11—PROTOZOAL INFECTIONS AT KANKAKEE

	No of Cases	Amebæ Present				Flagellates		Amebas and Flagellates
		Active	Encysted	Total	Per cent	Total	Per cent	
First examination	181	19	9	28	15.5	27	14.9	7
Second examination	104	21		21	20.2	23	22.1	7

Of the twenty-eight showing amebas at the first examination, only eleven were available for the later investigation and in these amebas were found only in three cases At the second examination, amebas were found in eighteen cases which had previously given negative results It should also be noted that where amebas and flagellates were found together these cases have been included also in the totals for the two types of organism given separately

Attention was also paid to the relationship between the presence of amebas at the first examination and the action of the bowels, the results being given below in percentages

No of Cases	Normal Stools	Diarrhea	Constipation	Alternating Diarrhea and Constipation
28	75.0	10.7	7.1	7.1

The following conclusions, therefore, seem to be justified

1 Of 181 recently admitted cases, 15.5 per cent showed amebas in the stools, which apparently belonged to the group described as *E tetragena*

2 One hundred and four of these cases re-examined later showed 20.2 per cent of amebas

3 The percentage of infected individuals apparently increased with the term of residence in the Kankakee State Hospital

4 In all probability the majority of these organisms are non-pathogenic

## BLOOD

Results of blood examinations in pellagra have been published by many different authors without the demonstration of any changes which are in any way constant or characteristic. Points which have chiefly been emphasized in regard to the cytology are the occurrence of a high

TABLE 12—RESULTS OF BLOOD EXAMINATIONS

	Age	Yrs in Hospital	Red Cells per c mm	Hemoglobin in gm per cent	Color Index	White Cells per c mm	Per Cent					
							Polymorphon Neutrophils	Small Lymphocytes	Large Lymphocytes	Mononuclear Leukocytes	Transitional Cells	Eosinophils
W H	62	8	4,248,000	13.44	1.12	12,500	39.8	12.6	17.0	25.0	1.0	4.0
W S	44	19	4,696,000	16.86	1.27	8,160	65.2	10.4	11.2	9.2	1.6	2.2
C S	56	19	4,845,000	15.88	1.15	10,540	59.0	13.8	9.4	6.8	2.2	2.8
L R	45	24	5,442,000	17.3	1.13	8,250	55.8	15.2	14.4	5.8	1.6	7.0
J H	50	12	5,836,000	16.8	1.02	11,380	60.0	14.8	11.6	9.8	1.0	2.6
S S	52	19	5,036,000	13.92	0.98	8,120	63.8	14.8	10.2	8.0	1.8	1.2
C H	60	39	4,800,000	13.92	1.03	12,200	54.0	13.6	12.2	17.2	1.8	2.0
A S	46	26	2,566,000	10.26	1.11	10,400	66.4	17.0	11.6	1.0	0.4	1.2
B S	68	8	4,936,000	12.96	0.94	7,280	62.6	12.2	11.0	10.6	1.2	1.8
W V	39	12	6,016,000	16.8	1.00	10,640	56.0	14.4	6.8	11.4	2.0	8.8
D N	72	25	4,640,000	14.40	1.04	7,440	58.2	12.0	8.0	11.4	3.0	6.6
J S	45	25	4,816,000	12.44	0.91	10,540	63.2	10.2	7.6	10.0	1.4	7.2
J D	55	18	4,528,000	11.04	0.87	13,800	65.2	11.4	7.6	10.4	3.4	1.4
B S	62	12	5,848,000	14.40	0.88	6,800	73.8	8.0	5.0	8.0	3.2	1.8
S L	38	7	6,288,000	15.36	0.85	11,440	78.2	6.4	3.8	3.6	4.0	3.2
C C	36	14	4,220,000	12.44	1.06	12,960	75.0	9.0	4.4	7.0	2.8	1.2
B M	50	21	4,696,000	13.92	1.05	13,700	71.4	9.8	6.0	6.2	4.6	2.0
A B	43	7	4,116,000	12.00	1.04	8,380	67.6	11.6	7.8	6.0	5.8	0.4
L P	23	3	4,880,000	12.44	0.91	8,160	50.0	11.0	7.0	18.6	9.4	3.4
H H	63	21	4,496,000	11.52	0.94	10,720	76.8	6.2	3.2	6.5	3.8	2.6
E L	74	1	4,352,000	11.52	0.94	13,120	57.0	22.0	3.0	9.6	6.0	1.8
L M	52	14	4,992,000	12.96	0.92	9,200	65.0	13.8	7.2	8.6	2.8	2.4
M D	46	18	4,328,000	11.04	0.91	15,000	56.0	10.4	5.2	20.4	0.0	1.0
A K	44	9	5,048,000	13.92	0.98	12,140	70.2	11.0	8.4	7.4	1.2	1.8
O L	66	2	6,080,000	12.00	0.71	7,860	41.6	18.8	8.4	16.4	6.0	7.0
Average	51	15	4,872,000	13.62	0.99	10,416	61.7	12.6	8.4	10.2	2.7	3.2
Maximum	74	39	6,288,000	17.3	1.27	15,000	78.2	22.0	17.0	25.0	9.4	8.8
Minimum	23	1	2,566,000	10.26	0.71	6,800	39.8	6.2	3.0	1.0	0.0	0.4



color-index and an increase in the proportion of mononuclear leukocytes. Leukocytosis has occasionally been observed but as a rule is absent. In reading the results of blood counts on most of the cases examined in this state it must be remembered that we are dealing, in the main, with individuals who were not normal before the onset of the pellagra. Blood changes are found in many of the chronic insane and this fact should be borne in mind in considering the examinations of such individuals who subsequently become pellagrins.

TABLE 13—BLOOD EXAMINATION OF PELLAGRINS DURING THE ACUTE OR SUBSIDING STAGES

	Red Cells per c mm	Hemoglobin, gm Per Cent	Color Index	White Cells per c mm	Per Cent							
					Polymorph Neutrophils	Small Lymphocytes	Large Lymphocytes	Mononuclear Leukocytes	Transitional Cells	Eosinophils	Eosophils	Unclassified
J B	4 088,000	11 52	1 0	7,400	54 20	28 33	5 66	4 21	0 59	5 59	1 22	0 18
N A	5,032,000	10 56	0 76	6,620	69 6	14 07	10 2	2 22	1 11	1 16	0 37	0 0
C G	4,205,000	11 52	1 0	6,400	47 33	33 83	10 5	3 17	0 33	2 00	1 16	0 0
J S	5,200,000	12 0	0 82	9,000	60 43	25 96	4 3	1 37	0 58	7 0	0 19	0 0
C A	3,960,000	11 5	1 3	9,600	64 46	29 15	3 2	0 0	0 0	2 96	2 3	0 0
J S	3 652,000	10 06	1 0	7,600	66 0	21 0	6 0	2 4	1 5	3 1	0 0	0 0
E S	4,664,000	13 9	1 06	7,400	61 43	20 28	12 6	2 57	1 86	1 0	0 29	0 0
J N	5,120,000	9 6	0 7	7,200	31 78	34 68	17 1	1 36	1 16	13 4	0 58	0 0
	4,542,000	9 6	0 76	7,000	38 0	50 4		4 8		6 8	0 58	0 0
	4,682,000	10 8	0 8	7,200								
J V	4,640,000			16,920	78 0	15 0	0 0	5 0	0 0	2 0	0 0	0 0
Average	4,524,864	11 1	0 97	8,394	57 22	34 22		3 42		4 5	0 67	
Maximum	5,208,000	13 9	1 3	16,920	78 0	51 78		5 0		13 4	2 3	
Minimum	3,632,500	9 6	0 7	6,400	31 78	24 27		0 0		1 0	0 0	

With this in view it was thought well to tabulate for comparison the blood findings in a group of individuals suffering from chronic mental disorder and comparable in that respect with the great majority of available pellagrins. They include cases of senile dementia, dementia præcox and defective mental development. The results of twenty-five such examinations performed by Dr. Addison Bybee, late clinical pathologist to the Psychopathic Institute, are given in Table 1. These cases were selected for the reason that in age, type of mental disorder and long residence in hospital they fairly correspond with the bulk of the population of the Peoria State Hospital.

It will be observed that in twelve of these the color index is normal or slightly above in spite of the fact that some of these show a diminished number of red cells. The two cases presenting the smallest number of red cells, viz., 2,566,000 and 4,116,000 have, respectively, a color index of 1.11 and 1.04. With regard to the proportions of the different varieties of white cells it will be seen that on an average also the relative number of large mononuclear leukocytes and transitional cells is somewhat high. Attention should be called to the presence of eosinophilia in several of the cases.

In Table 13 will be found the results of eleven examinations made on nine different patients during the acute or subsiding stages of pellagra.

It will be observed that in five of these the color index is at or slightly above the normal, although in all five the number of red cells is more or less subnormal. In only one patient, J. V., was there any leukocytosis. This patient, reported in more detail below (Case 2), was apparently not insane before the onset of pellagra. The number of leukocytes increased at subsequent examinations from 16,920 to 20,480 per cmm. The attack was very severe, with fatal result, and at necropsy no evidence of any septic focus was found to account for the leukocytosis with absolute and relative increase in the polymorphonuclear leukocytes. One must therefore conclude that this was due to pellagra. Apart from this case all other patients have shown a relative lymphocytosis and there is apparently a diminution in the proportion of large mononuclear leukocytes. It will be observed that the increased number of lymphocytes was not limited to the larger varieties, so that it cannot be explained by differences in nomenclature and a confusion between large lymphocytes and large mononuclear leukocytes. Eosinophilia is also present in five of the nine cases. In one of these patients, J. N., the proportion is as high as 13.4 per cent and it may be noted that this patient also showed amebas in the stools. The eosinophilia, however, does not always correspond with amebiasis as, for instance, in J. B. no amebas were found. In view of the findings in Table 7, however, one need not be surprised at these figures.

A blood count of the patient, J. N., made eighteen months after the disappearance of all pellagrous symptoms at a time when the patient was apparently in good health and had had no recurrence, gave the following results: Red cells, 4,720,000 per cmm, hemoglobin, 11.5 per cent, color-index, 0.87, white cells, 8,200 per cmm, of which 50.5 per cent were polymorphonuclear neutrophils, 42 per cent lymphocytes, 1.5 per cent mononuclear leukocytes and transitional cells, 5 per cent eosinophils and 1 per cent basophils.

Besides these enumerations several weeks were occupied in the careful study of blood both in the fresh state and after staining by various

methods The fresh blood was examined with direct illumination and the dark-field illuminator The stains employed have been those of Jenner, Giemsa, Levaditi and methylene blue In no specimen has anything been observed which seemed to be in any way abnormal

Cultures were made from the blood in several cases with negative results, except in one instance, J N, at the Kankakee State Hospital In this case a large motile bacillus was obtained which grew freely but somewhat slowly on all media. That it was not a contamination seemed to be proved by the fact that the organism was agglutinated by the patient's serum No clumping was obtained, however, with the sera of other pellagrins or healthy individuals and the bacillus gave no evidence of pathogenicity even in large doses when injected into a monkey and a guinea-pig We are therefore inclined to regard this as evidence only of a lowered resistance to the invasion of the individual by parasites

Similar investigations carried out at Peoria by Captains Nichols and Siler gave results which are reported by them as follows

Blood cultures and spinal-fluid cultures were made from ten living cases, and cultures from the spleen were made in six cases at autopsy In every instance the results were negative

The greater portion of two weeks was devoted to the examination of fresh blood and spinal fluid, and smears from the blood, spleen, and liver The smears were stained with the Leishman ptyochrome stain, with Giemsa's polychrome stain, and with Mac Neal's polychrome stain Nothing whatsoever suggestive of a protozoal infection was encountered

Blood cultures were made on blood-agar (trypanosome media), the results in each instance being negative

#### URINE

Specimens have been examined repeatedly from the patients transferred to Kankakee from Peoria and also in cases arising in the former institution No constant changes have been found with the exception of a very marked indican reaction which was present in all and can probably be correlated with the intestinal putrefaction In a few instances a trace of albumin and a few hyaline casts have been present

One striking feature also has been the great variability in quantity, color and specific gravity of the specimens obtained on various days from the same patient In the case of J N, who passed through a very severe attack, these variations were remarkable and are recorded in graphic form on Chart 2 It should be stated that the estimations of chlorids, phosphates and sulphates were made by the Purdy centrifuge method and hence cannot be regarded as accurate Nevertheless, since they were all made with the same centrifuge revolved for the same length of time, a comparison between the readings for the different days

is quite permissible. These results cannot be regarded as indicating anything more than evidence of great disturbance in metabolism and suggest the advisability of more exact study of the exchanges.

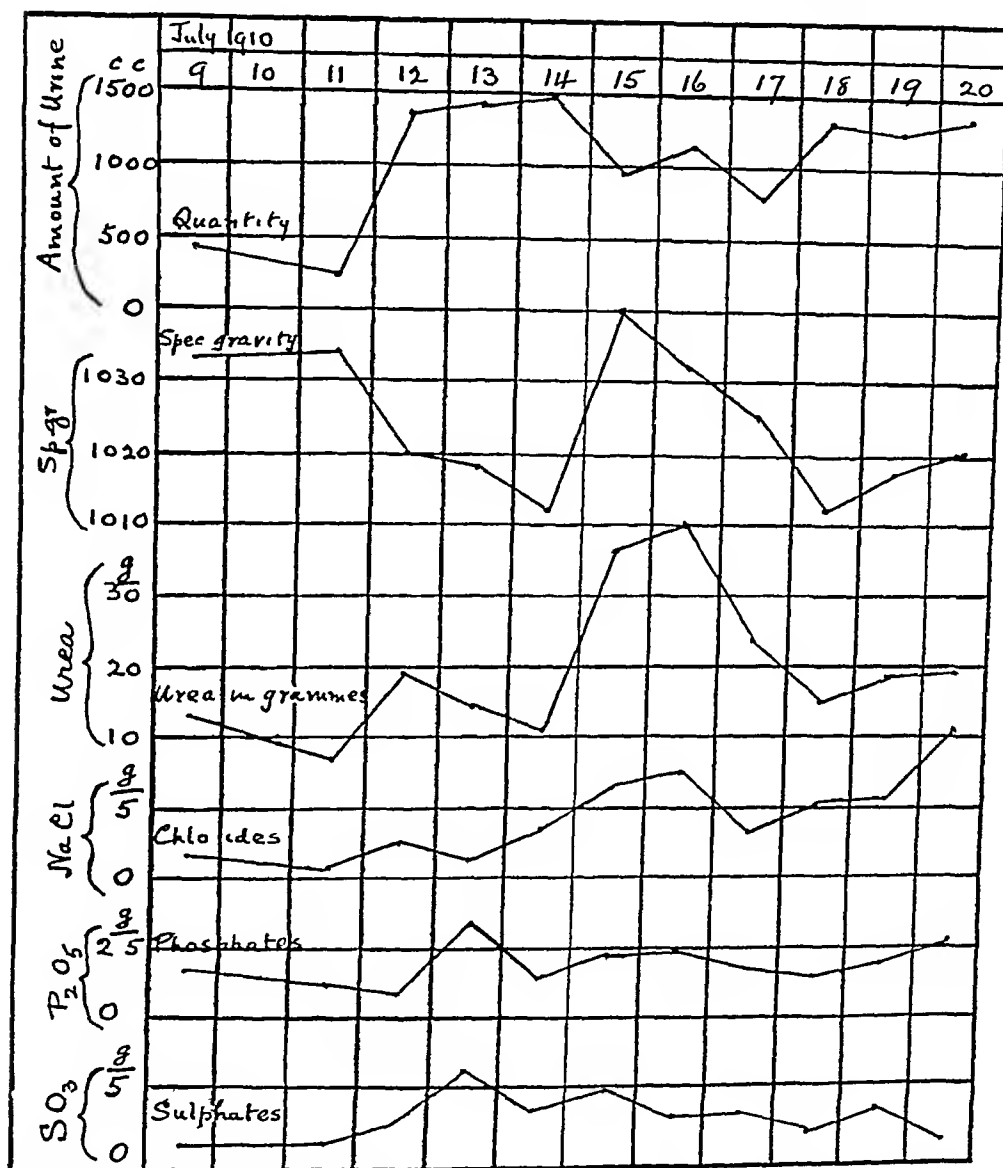


Chart 2—Showing variation in quantity, color and specific gravity of urine on different days in the case of J. N.

#### THE COURSE OF THE DISEASE

The great majority of cases have shown an acute course with sudden onset and have arisen for the most part in individuals of poor physique, although some few have been well nourished and apparently healthy. As a rule the earliest symptom observed has been the skin eruption on the hands with simultaneous or rapidly succeeding soreness of the mouth and more or less diarrhea. This acute phase lasts for one or

two weeks and then gradually subsides with the replacement of the erythma by a thickened, dry, scaly condition of the skin which may last several weeks or even months, during which desquamation occurs.

A certain proportion of the cases have begun with gastro-intestinal symptoms, consisting of chronic and often severe diarrhea with more or less stomatitis. At this stage the diagnosis is very difficult to make and cases have been observed in which these symptoms have been present for one or two months before the appearance of the characteristic rash. The eruption has appeared suddenly and has generally been very severe with marked bleb formation and ulceration. These cases, in our experience, have been extremely fatal, the patient rapidly losing flesh and becoming weaker. We are inclined to regard the occurrence of severe mouth symptoms in any case as of very grave import. Nevertheless in some cases in which death has seemed to be only a question of a few days, improvement has occurred with an apparently complete recovery. One such example, J N, at the Kankakee State Hospital, where death was momentarily expected in the spring of 1910, made a good recovery and has had no recurrence up to November, 1911, being apparently in fully as good health as before the attack. This patient, though not robust was nevertheless in a good state of nutrition and health before the onset of the pellagra.

Another form of course deserves to be especially mentioned because it touches on the important question as to what constitutes pellagra and when it may be considered as recovered. In these cases the gastro-intestinal symptoms are usually severe and there is consequently progressive emaciation and exhaustion. After a few weeks the skin lesions disappear and the mouth may get well, diarrhea becoming less or even disappearing, and yet the patient does not improve or only slightly and then temporarily. Without any recurrence of the acute symptoms of pellagra there is a gradual decline with increasing evidence of involvement of the nervous system until the picture becomes unmistakably that of central neuritis which ends fatally in a short time (See case J V below).

In some instances these symptoms have occurred within a few days of the subsidence of the characteristic pellagrous phenomena or even while they are still present, whereas in others they have been delayed for several months. We do not feel justified in expressing any definite opinions on the meaning of this condition but it may be suggested that the sequence is somewhat similar to that which occurs in diphtheria in which a peripheral neuritis follows at a longer or shorter interval after the actual infective agent has been eliminated. Yet it is unquestionably due to the action of the toxins, produced by the organisms, on the peripheral nervous system. In pellagra the

neuritis is more particularly central, but may well be a late effect of the toxins, whatever their nature, as in diphtheria, and does not necessarily indicate that the disease is still active. Progressive emaciation and exhaustion after the subsidence of the characteristic manifestations of pellagra, have been noted by many authors and have been regarded by some as evidence that the disease is still active. We are unable to say whether all such cases present symptoms of central neuritis or not, as the necessary data are not available. Attention to this point is certainly desirable, as it offers the possibility of a definite explanation for this otherwise puzzling course.

It is usually stated that in most cases after the subsidence of an attack the patient regains his health more or less completely and may seem to be entirely recovered, but with the appearance of the next spring or autumn there is a recrudescence of the active symptoms. The short time during which cases have been under observation in this state renders it impossible to give any very reliable data concerning this question, but it may be stated that many of the patients showing attacks in 1909 and 1910 have not presented any recurrence up to date, although they have been closely watched. The actual figures are given in the statistical study. Of the six cases transferred from the Peoria to the Kankakee State Hospital in July, 1910, selected for the reason that they presented unquestionable symptoms of pellagra, none up to the end of November, 1911, have shown any further symptoms of the disease. (One of these patients died from pneumonia April 15, 1911.) The best marked example of annual recurrence was seen in the city of Peoria by the courtesy of Dr J H Bacon,<sup>2</sup> as already referred to. This patient had had seven attacks in seven years although the diagnosis was not made until the seventh and fatal attack in March, 1910.

Finally there are to be mentioned cases which present a much more chronic course as regards the individual attacks. In these cases there is, as a rule, but little constitutional disturbance and the initial erythema is slight or may not be seen at all. There occurs, however, a slowly increasing pigmentation with some thickening and roughness of the skin of characteristic distribution, symmetry and outline. The color in these cases becomes extremely dark, often almost black, and persists for some months, when desquamation occurs and the skin gradually resumes a more normal color. This condition has only rarely been observed among the cases in this state and is perhaps more difficult of diagnosis, especially when it occurs in old people, than the more acute forms.

#### PATHOLOGICAL FINDINGS

The post-mortem findings in so far as they have yet been worked up are described in detail below in connection with the descriptions of the cases. While it cannot be said that there is anything specific about the

changes found, yet there are certain features which seem to be constant and open up certain more or less definite lines for future search. These may be summarized as follows:

1 The *nervous system* presents a picture of axonal chromatolysis involving especially the Betz and larger pyramidal cells of the precentral convolutions and the cells of the nuclei in the cerebellum, pons, medulla and cord as well as the posterior root and sympathetic ganglia. Besides these changes numerous cells in most cases show a marked pigmentary degeneration of fatty nature similar to that found in the senile nervous system and in some other conditions. With this there is, in most cases, but little evidence of connective tissue reaction, and we would especially emphasize the absence of infiltration of the perivascular sheaths. In some cases there is more or less overgrowth of glia cells along the vessels and around the nerve cells. The picture here described is identical with that published by others, notably Spiller and Anderson, in cases of pellagra, but is also strikingly similar to the picture of central neuritis. This similarity, indeed, led us to ask whether the patient did not have the clinical picture of that condition before we were aware that Dr. Wilgus, superintendent of the Elgin State Hospital, had already observed and commented on it.

Central neuritis, like peripheral neuritis, must not be regarded as a disease *suu generis*, but merely as a type of reaction on the part of the nervous tissue, capable of being produced by various harmful agents. In response to a letter, Dr. Adolf Meyer, who first described the changes which bear this name, writes that he is not surprised to hear that they are found in the end stages of pellagra and gives the interpretation contained in the above words:

2 The *liver* has been constantly the seat of small islets of a low-grade inflammation of the portal connective tissue lying in the interlobular septa. The intralobular capillaries are engorged and in most cases there are many small blood extravasations. The liver cells have undergone fatty degeneration which is in some instances remarkable, and the change is distributed in every case along the periphery of the lobule. This, in the absence of any marked cirrhosis, at once suggests that there may have been some toxin circulating in the portal blood-stream. Some of the specimens even suggest a picture of a very early stage of acute yellow atrophy or the more acute forms of alcoholic cirrhosis.

3 *Intestinal* ulceration has been present in three out of seven cases. This has not the acuity of an amebic infection and no amebas have been found in the walls. Even where no ulceration was found a low-grade infiltration of the mucosa and submucosa has been present in places

These findings are certainly of interest in relation to the condition of the liver

4 The *kidneys* show degenerative changes in the renal epithelium and in all cases more or less interstitial nephritis, in spite of the fact that the ages in some of the cases is certainly not great. Engorgement of capillaries with small hemorrhages are also frequent

5 The *spleen* shows some fibrous overgrowth and again small hemorrhages

6 Pigmentary changes are present in the *heart muscle* at an age which is below that at which they are usually found

7 In some of the cases hyaline changes in the intima of the blood-vessels has been marked, but this is not constant

All these appearances suggest the presence of some toxic substance in the blood. One may even go further and from the changes in the intestine and especially in the liver, suspect that this toxin originates in the intestine and enters the circulation by way of the portal system. The great frequency of gastro-intestinal symptoms during the clinical course of the disease might be regarded as pointing in the same direction. There is always, however, to be borne in mind the possibility that these changes may be secondary to the pellagra. That is to say, that as the result of the gross disturbances in metabolism and vital resistance, which certainly accompany the disease, there may follow a secondary invasion of the intestinal tract with organisms which then give rise to the changes found by virtue of the toxins elaborated during their growth. Secondary changes such as this would be quite in accordance with what is found in other diseases

If, however, we look for evidences of the localization of a blood-borne parasite in other parts of the body we find entirely negative results. The nervous system does not present any features similar to those found in such diseases as trypanosomiasis or parasymphylis. The absence here of any focal changes and of perivascular infiltration are strikingly different from the conditions found there. The picture presented is much more that of a diffuse toxic state than of one due to a blood infection. The only tissues in which there seemed to be any focalization of lesion were in the intestinal wall and the liver. In this latter organ the areas of infiltration present in the interlobular septa were decidedly local and often widely separated, and where found, existed in the form of more or less circumscribed islets. There was no generalized invasion of the whole of the connective tissue. The intensity of the infiltration was certainly of low grade and did not suggest a very acute inflammation.

As already indicated, the study of degeneration in the nervous system is very incomplete, but from what has been seen so far there is no evidence



of any system degeneration. The fibers in the cord which stain by the Marchi method are scanty and widely scattered and there is nothing to support the suggestion made by Long that the nerve roots are pressed on as they pass through the intervertebral foramina. It might also be mentioned that the distribution of the skin lesions does not correspond with that of the posterior roots of the cord. The perfect symmetry so characteristic of the skin lesions in pellagra is hardly conceivable as the result of any gross nervous lesion and suggests far more some generalized noxious agent which is capable of a far finer biochemical selective power than could possibly be conceived from pressure or other gross lesion of like kind.

Pellagra is sometimes described as a disease especially involving the nervous system. From the findings here described the nervous system seems to be involved only as a secondary process and at a late stage of the disease, in this respect confirming the opinion expressed above from clinical study.

Without expressing any opinion as to casual relations, it seems to us that the main indications revealed by the pathological study point to the need for closely following up investigations on the intestinal tract. At the same time we can admit that this *habitat* would not contradict the hypothesis that the parasite has entered the system through the blood stream as the result of bites by insects.

#### CASE REPORTS

**CASE 1**—*Pellagra in a Previously Healthy Woman Which Without Improvement in the Specific Symptoms Led to Death in Three Months*

**History**—A D., a white female, aged 43, seamstress by occupation and a widow. She is said to have been a healthy woman, though always in poor circumstances and during the last few months has had a hard struggle for existence. She has four living children and had one stillbirth but no miscarriages. The menopause occurred five years ago. Her only illnesses during adult life have been gonorrhea "several years ago" and malaria "on several occasions." She had been living in Corinth, Mississippi, for "several years" until June, 1910, when she came to Chicago, where she has been since. Previous attacks of pellagra are denied.

**Present Illness**—Present illness began in October, 1910, the first symptoms being "chapping of the hands" with diarrhea and progressive emaciation. The hands became raw and fissured and this was accompanied by pain of a burning character. Diarrhea has been very profuse and for two months there had frequently been blood in the stools, sometimes in the form of clots. The mouth also became very sore, rendering eating difficult and there was profuse salivation. In spite of this she showed a craving for food, the ingestion of which would often give rise to "cramps." No definite mental symptoms have been noted with the exception of a change in temperament, in that she was more fretful and irritable than usual. At no time has there been any evidence of "wandering in her mind."

**Examination**—She was admitted to the Cook County Hospital Jan. 12, 1911, under the care of Dr. W. A. Pusey, to whose courtesy we are indebted for permission to use this case. At this time she presented an extremely emaciated condition with incessant diarrhea. Mentally she was clear and remained so until

the time of her death, but was listless and apathetic. Some degree of depression was present but this did not seem to exceed the limits justified by her condition. She answered questions clearly and readily and her memory seemed to be good, although the examination was not very thorough.

On the backs of the hands extending upwards to about 2 inches above the wrists and forming a cuff around the wrist was a characteristic pellagrous eruption completely symmetrical on the two sides. The skin over this area was deeply pigmented, fissured and excoriated, with yellowish exudate between the roots of the fingers. The mucosa of the lips, tongue and inside the cheeks was markedly red, swollen and partially denuded, with yellowish exudation where the lips came in contact with the teeth.

The diarrhea continued with great severity, accompanied sometimes by the passage of blood and the patient rapidly became weaker. She was first seen by us on Jan 20 1911, at which time she was so weak and ill that an exhaustive examination was not permissible. She rapidly became tired when talked to, the swelling of the mouth and tongue rendering it difficult for her to converse. She, however, seemed to be clear and gave some details concerning her illness without hesitation or error. She was not unduly depressed but realized that she was dying and was very willing to permit any examination which would help to elucidate the disease which she recognized as being somewhat rare. The knee-jerks were greatly exaggerated but equal on the two sides, yet did not appear to be more marked than is commonly found in advanced exhaustion. The plantar reflexes were both of flexor type. Rough testing revealed no gross changes in sensibility of the skin.

Blood was taken by venipuncture for agglutination and complement fixation tests. The stools were also examined for amebæ but none were found.

*Necropsy*—Death occurred Jan 22, 1911, at 1 30 p m and an autopsy was performed the following day at 11 a m. At this time the pellagrous eruption was still well-marked and the evidences of excoriation in the mouth were quite distinct. On section the lungs showed considerable edema, especially at the bases. There was a healed calcareous scar at the right apex, but otherwise no change. The pericardium contained some excess of clear fluid but the heart and vessels showed no notable changes. The heart muscle was somewhat thin and flabby and there was no hypertrophy of the left side.

The kidneys showed some evidences of early chronic interstitial nephritis. The adrenal bodies were firm, each weighing 4 g.

The spleen was larger than normal (weight 200 gm) and its substance seemed to be unduly firm, but there was no evidence of great increase in fibrous tissue.

The intestinal tract appeared normal everywhere with the exceptions of the mucosa of the mouth and the lower part of the sigmoid flexure in which were found about ten small, roughly circular, ulcers from 2 to 8 mm in diameter. These ulcers were all situated within a length of about 2 inches. The edges were somewhat heaped up but not undermined. The surface was rough. The mesenteric glands were also enlarged but on section showed an approximately normal appearance.

The liver was engorged with blood and its section showed an obviously fatty appearance.

The pelvic organs presented nothing abnormal but the mucosa of the vagina was very red and somewhat swelled, especially in the region of the fornices.

The central nervous system presented no very definite changes, with the exception of some increase of fluid over the convexity of the brain.

Portions of all organs were removed for microscopical examination, and one hemisphere of the brain was sent to the University of Chicago for chemical examination by Dr Waldemar Koch.

#### MICROSCOPICAL EXAMINATION

**Lungs** The lungs show nothing abnormal beyond general extreme congestion.

**Heart** Heart muscle shows no increase in fibrous tissue. The blood vessels are engorged and here and there are to be seen small extravasations between the

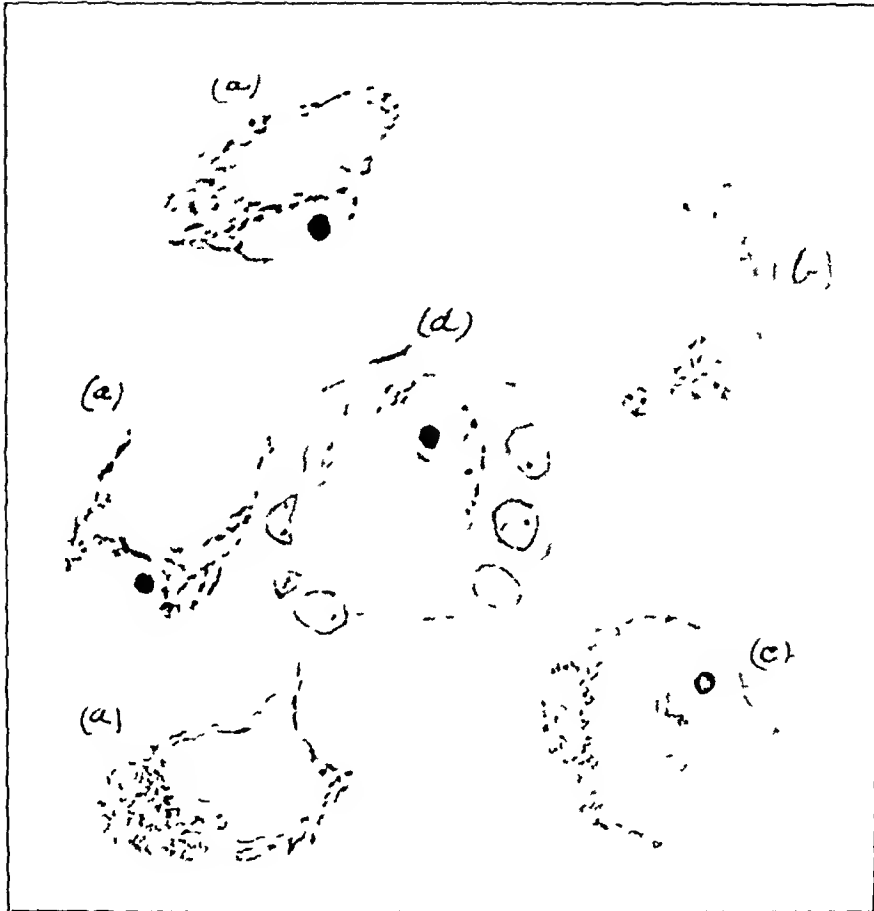


FIGURE 3—Case A D Nerve cells showing chromatolysis and pigmentary changes, (a) from Clarke's column, (b) from ant central convolution (c) from ant cornu in cervical region, (d) from post root ganglion



muscle columns. The muscle cells stain diffusely with a granular appearance. In places vacuoles are found within the cells and in many of them there are small collections of greenish-yellow pigment around the nuclei. The muscle cells also show a tendency to fragmentation.

**Kidneys.** The capsule is moderately thickened and there is some increase of fibrous tissue between the tubules and also of Bowman's capsule. There is marked congestion of the vessels, especially in the medullary rays, with here and there small hemorrhages which are more numerous close beneath the capsule and in the medullary rays. The cells of the convoluted tubules are swollen, granular, and their outline is indistinct, while their nuclei stain rather poorly as compared with those of the smaller tubules. The glomeruli are congested but well stained and show no changes in the vessel walls. There is no denudation of epithelium. There is a moderate amount of small round celled infiltration close beneath the capsule but this is not noticeable elsewhere.

**Spleen.** Moderate overgrowth of connective tissue involving the capsule and trabeculae. The pulp is engorged with blood and there are a few small areas in which the blood cells are undergoing disintegration, which probably represent small hemorrhages.

**Suprarenal Glands.** The cells in the glomerular layer are well stained but show small vacuoles of fat which become more marked in the fascicular layer. The vessels are all engorged, especially in the fascicular layer where there are several minute hemorrhages. A similar appearance is observed in the reticular layer. The central veins are widely dilated.

**Liver.** The capsule is slightly thickened and there is a very moderate increase of fibrous tissue in the portal canals. In this latter there is also an infiltration with small round cells, moderate in degree. The blood vessels are extremely dilated and this dilatation becomes greater as the capillaries approach the central veins of the lobules, in many places the width of these capillaries being greater than that of the liver cell columns themselves. Close beneath the capsule there are a number of small extravasations of blood. The parenchyma is well stained but there is marked fatty degeneration of the cells around the periphery of the lobules, many of the cells appearing to consist of a large fat droplet. In some lobules there is also fatty degeneration of the cells near the center, although this is nowhere very marked. The bile ducts are well stained and not increased.

**Pancreas.** The pancreas shows a marked engorgement of the blood-vessels with very slight increase in fibrous tissue, but otherwise no change.

**Intestinal Ulcers.** Serial sections made through one of these ulcers showed a somewhat subacute type of inflammation with increase of fibrous tissue elements and moderate small celled infiltration. A careful search was made for the presence of amebas in the ulcer wall and sections were submitted to Captain Nichols of the Army Medical School, Washington, D. C., who examined them in collaboration with Dr. Neate, microscopist to the Museum of the Army Medical School. They report that they 'have been unable to satisfy ourselves that they contain any amebas. The general picture, too, does not seem to be active enough for an amebic ulceration.'

Besides the ulcers, similar infiltrations of the submucosa and even deeper than the muscularis mucosae were found in the apparently healthy wall of the intestine.

**Mesenteric Lymph-Nodes.** These on section showed marked engorgement of the vessels with blood and some dilatation of the lymph-spaces but there appeared to be no increase of connective tissue and no other pathological changes.

Sections of the *ovary* and *tonsil* revealed nothing worthy of special note.

**Central Nervous System.** The pia mater showed no changes either with regard to its connective tissue or blood vessels.

**Nerve Cells (Fig. 3).** Sections were examined from various regions of the cortex and also from different levels in the cord and medulla. Stained with methylene blue and cresyl violet, marked chromatolytic changes of an axonal type were found in the large pyramidal cells of the Rolandic region but especially of the Betz cells. Of these latter practically all show extreme changes. The

cells are swollen and stain faintly, the nucleus is displaced and the nucleolus often stains poorly. The Nissl granules have largely disappeared, small collections of them remaining at the base of the larger processes, along the edges of the cells, and often collected as a small mass around the nucleus. Very many of these cells show masses of a yellowish green pigment, sometimes almost filling the larger part of the cell. This pigment stains black with osmic acid. The large pyramidal cells show somewhat similar changes, especially in regard to the pigmentation, but the chromatolytic changes are not so marked and many healthy cells are still present.

In other regions of the cortex an occasional larger pyramidal cell is found showing evidences of chromatolysis but they are nowhere very marked. The Purkinje cells of the cerebellum show generally a somewhat poor content of chromophil granules but are not otherwise changed. The dentate nucleus shows many cells with chromatolysis.

In the medulla oblongata the cells of practically all nuclei show marked chromatolytic and pigmentary changes, especially in the larger types of cells.

In the spinal cord similar changes are found in some anterior horn cells at all levels examined, but the great majority of these cells appear healthy. The most marked changes were found in the cells of Clarke's column where the majority of them were undergoing chromatolysis and pigmentary degeneration. Chromatolytic changes were also found in the cells of the posterior root ganglia. In specimens stained by the Marchi method the pigment deposits both in anterior horn and Clarke's column cells are very evident.

**Marchi Method.** Brain sections by this method have not yet been studied but in the spinal cord there are a few degenerated fibers scattered diffusely through the white matter. This does not especially involve the pyramidal tracts. Degenerated fibers are also present in both anterior and posterior spinal roots.

**Glia and Vessels.** The absence of any increase of glia cells is very striking. Not more than one or two satellite cells are found in relation with the degenerated cells, and the glia nuclei are nowhere more numerous than normal except possibly around some of the larger vessels. The cerebral vessels show in places a slight increase of the adventitial nuclei but there is absolutely no infiltration of the perivascular sheaths. This is true in all sections examined and certainly forms a striking contrast to the pictures seen in syphilis, parasymphylitis and trypanosomiasis.

Attention may also be called to the large number of corpora amylacea which are present in the spinal cord, situated especially along the course of the posterolateral septa and along the borders of the anterior fissure. In these regions as many as ten or twelve may be seen in the field of a 4 mm objective. When the age of this patient (43 years) is considered the pigmentary changes and corpora amylacea must be regarded as definitely pathological.

Chemical examination of the right cerebral hemisphere by Waldemar Koehl, Ph.D., of the University of Chicago showed a diminution of the ventral sulphur fraction without change in the total sulphur. Such a condition as this has been found hitherto only in the brains of individuals who have suffered from dementia praecox. There was no change in the phosphorus content.

**CASE 2—Pellagra in a Patient of Psychasthenoid Personality Accompanied by Disorientation, Perplexity and Some Anxiety with Hallucinations. Generalized Eruption One Month After Onset. Disappearance of Active Pellagrous Symptoms and Simultaneous Mental Improvement But Without General Recovery. Development of Central Neuritis Two Months Later. Death Four Months After Onset.**

J. V., white female, housewife, aged 57, married.

**Family History.**—This was meager, but showed nothing of importance.

**Personal History.**—Information concerning her early life was not obtainable. Within one week of her marriage at the age of 29 she was noticed to have psychasthenoid symptoms. She has had a very hard life, having to assist in earning a maintenance for her family of four children. Her husband left her in 1905 to take up some land in Wisconsin, the patient after much querulous heart-

tion refusing to live there with him, not because there was any quarrel but because she could not stand the desolate surroundings. During the whole of her married life she was irritable, unable to make up her mind to do things and would worry over them when they were done. Such hesitation and indecision have characterized all her acts, even in relation to minute details, such as cooking food, etc.

She has lived at Mazon in Grundy County, Illinois, ever since her marriage, with the exception of a short visit to her husband in Wisconsin and to a daughter in Kansas City, Missouri. She returned from this latter trip about December, 1909, and has been living in Mazon since. She has been a semi-invalid for many months and was operated on in October, 1910, for a fistula and ischio-rectal abscess. She was more irritable and unable to make up her mind during this time than before but there were no other definite evidences of mental disturbance.

No history of any eruption suggestive of an attack of pellagra in the past could be obtained.

*Present Illness*—At the end of April, 1911, she developed an "eczema" of the hands with severe diarrhea and about the same time she seemed to go "out of her mind." She did not know at times where she was and spoke of seeing smoke around the house. She recognized people, however, and seemed better when visiting in other homes than she did in her own. She became rapidly weaker, more fretful and seemed more dazed. No evidences of apprehension or further hallucinosis were noticed.

*Physical Examination*—She was admitted to the Kankakee State Hospital May 13, 1911, when she was found to be much emaciated, with a well-marked pellagrous eruption on the hands, severe diarrhea and raw, swelled tongue with much gingivitis.

Physical examination revealed no signs of other disease. The reflexes were increased equally on the two sides, the plantars being of flexor type. All movements were very feeble and there was some tremor of the fingers.

Mental examination showed her to be depressed and somewhat clouded. She was very restless and seemed anxious and worried. She mistook nurses for people whom she had known before, and answered most questions with "I don't know." She performed a number of acts of perplexity, such as pulling off her bed clothing and piling it on the floor, and she wandered about in a dazed manner. The pellagrous eruption on the hands was of extremely dark color, some fissures were present about the knuckles and desquamation was marked at the time of admission. The eruption rapidly disappeared, desquamation being practically complete by the middle of June, leaving a pink, rather delicate looking skin. The sore mouth also improved and was well in about one week after admission. Diarrhea was severe during May but disappeared after that time, when she became more or less constipated, with only one day in which there were four stools which could not be accounted for by purgatives.

May 25, 1911, there developed a red, blotchy eruption on the arms, which rapidly extended over the whole body, including trunk and lower extremities and was regarded as a generalized pellagrous eruption. In the course of a few days this rash turned brown and began to desquamate. Most of it had disappeared, leaving a healthy looking skin, within three or four weeks, but some desquamation was still present on the lower extremities at the time of death.

The confused, depressed, irritable state which was present on admission disappeared about the beginning of June, the period of delirium appearing to coincide with the acute pellagrous symptoms. After this time the patient became more cheerful, talking freely and gave a good account of her life without evidence of any mental dilapidation. There were, however, periods for two or three days at a time in which she would become depressed, entirely inaccessible, asking to be left alone, refusing food and saying she wished to die, but there was no recurrence of clouding of consciousness at these times. She explained these episodes by saying she felt so ill and wanted to go home to die.

Evidences of involvement of the *nervous system* gradually increased throughout the illness. The deep reflexes became more and more exaggerated until ankle clonus of short duration could be obtained on both sides. The Gordon paradoxical reflex appeared on both sides and finally a bilateral Babinski phenomenon. With this there was progressive weakness and wasting of muscle quite generally throughout the body.

Dizziness was a marked feature throughout the illness and she occasionally fell out of bed, apparently as the result of vertigo. In walking she was extremely unsteady and somewhat spastic, showing a constant tendency to fall towards the left.

No gross changes in skin sensibility were detected, with the exception that during the last two weeks of her life there seemed to be some blunting, but she was too ill to give much attention. At the time of the generalized eruption there was quite definitely increased tenderness of the muscles and nerve trunks which, however, disappeared in a few days.

During the last two weeks of her life there appeared *jaetatoïd movements* involving at first the four extremities, which became rapidly more and more violent extending even to the facial muscles, the lips, eyeballs and respiratory muscles. Accompanying this was an increasing tonic spasm of all muscles with slight retraction of the head. The *jaetatoïd movements* were sometimes so severe as to raise the patient completely off the bed. During this last two weeks she seemed to be clear, to take an interest in the presence of her daughter and son, but she often complained of an extreme dizziness and sometimes of noises in the ears like "flies." There was no vomiting at any time but the patient complained of nausea and cructations.

**Blood.** The blood was examined repeatedly both fresh and stained but no abnormal bodies were noted. Blood counts showed a moderate degree of secondary anemia, the red cells numbering from 4,640,000 to 4,148,000 per cmm, the hemoglobin being estimated at 85 per cent. The white cells at the first examination numbered 16,920 per cmm and increased to 20,480 at the end of June. All through there was an increase of polymorphonuclear leukocytes which comprised 75 to 79 per cent of the total. Small lymphocytes 15 to 19 per cent, large lymphocytes 2 to 5 per cent and eosinophils 1 to 2 per cent. No abnormal white cells nor red cells were observed.

**Urine.** Urine examination on several occasions presented no abnormalities and the stools were searched three times, after administration of calomel and magnesium sulphate, for the presence of protozoa. Active flagellates of the type of *Trichomonas intestinalis* were present each time but no amebas were found.

**Necropsy.**—Death occurred at 8 30 a. m., August 17, 1911, and an *autopsy* was performed at 10 30 a. m. the same day. At the examination the body was found to be extremely emaciated. The lungs showed nothing abnormal with the exception of passive congestion and some scars of healed tuberculosis at both apices. The heart showed nothing abnormal. There was a moderate amount of sclerosis in the aorta.

The kidneys presented a slight amount of interstitial nephritis. Spleen was injected but appeared otherwise normal. The suprarenal glands showed nothing abnormal.

The gastro intestinal tract was normal with the exception of three small ulcers in the lower part of the ileum just above the ileocecal valve. These ulcers were punched out with some heaping up at the margins but no undermining, and appeared to be healing.

The liver was engorged with blood and had a fatty appearance. Pelvic organs were normal with the exception of a submucous fibroid. The brain weighed 1,190 gm. There was micr gyrria of the frontal and to a less extent of the occipital lobes. The vessels showed some slight opacities and were injected. Portions of all organs were removed for examination microscopically and one half of the brain was placed in alcohol for chemical analysis.



## MICROSCOPIC EXAMINATION

**Lungs** The lungs show an increase of fibrous tissue with thickening of the vessels and moderate anthracosis

**Heart** Heart muscle shows some tendency to fragmentation but no fatty change. Some cells show pigmentation about the nuclei

**Kidneys** The capsule is thickened and there is some fibrous tissue between the tubules. The vessels are all engorged and a few small hemorrhages are scattered throughout. In places the arteries show marked hyaline degeneration. The glomeruli are small, the spaces about them dilated and the capsule of Bowman thickened. Some of the glomeruli show a marked increase in connective tissue nuclei. Beneath the capsule many areas show a moderate small celled infiltration. The epithelium of the tubules for the most part is well stained but in places that lining the convoluted tubules appears swollen and finely glandular. Many of the tubules contain a hyaline material and a few some epithelial cells

**Spleen** Capsule thickened with corresponding increase in the fibrous trabeculae. The organ is much congested and there are several hemorrhages with dark blood pigment

**Liver** The capsule is moderately thickened and there is a general increase in fibrous tissue of the portal canals. Around some of the smaller vessels in the portal canals there is also an infiltration with small round-cells. These stand out as rather widely separated islets in the section. The whole organ is markedly congested and there are a number of small hemorrhages especially beneath the capsule. The congestion of the lobules increases as the central vein is approached and here the columns of liver cells are widely separated. The liver cells stain well but there is extreme fatty degeneration of patchy distribution especially at the periphery of the lobules. Some of the cells nearer the central vein also show the fatty change, but to a less extent. The patchy distribution of this fatty change and of the small celled infiltration are striking and the same may be said of the capillary engorgement of the lobules, although this latter is more constant than the other two. The bile ducts are well stained and show no increase

**Pancreas** There is moderate increase of fibrous tissue in the pancreas and a few small hemorrhages are seen. Islands of Langerhans normal in number and appearance

**Small Intestine** Unfortunately no sections were obtained from the ulcers observed. The tissue containing them was badly fixed and could not be cut. Sections from other parts of the small intestine showed engorgement with blood and small celled infiltration of the mucosa and submucosa in irregular patches similar to those described in Case A D

**Thyroid Gland** This showed increased fibrous tissue with some epithelial hyperplasia, marked engorgement with blood

**Nervous System** Nerve cells, widespread chromatolysis of axonal type with marked pigmentary changes are found involving especially the larger elements. Pigmentary changes are present even in the medium sized pyramidal cells. These changes are most marked in the Rolandic regions but are present, though to a less extent, in other regions examined. Many of the cells, especially among the smaller elements also show a diffuse, dark staining which with the heaping up of satellite cells suggests the existence of a more chronic type of cell change. Similar changes are present in the Purkinje cells and the cells of the posterior root and sympathetic ganglia

The fatty changes are very obvious in specimens stained with Schiarch both in the central system and in the sympathetic. March specimens have not yet been examined

**Glia and Vessels** Contrary to the findings in the case of A D, there is marked increase in the number of glia nuclei in all regions of the brain. In many places the satellite cells form heaps and some of the vessels are bordered by solid rows of such nuclei. Glia nuclei are present in large numbers in all layers of the brain cortex and are increased also in the white matter

The adventitial sheaths of the arteries show multiplication of the nuclei and there is in places a proliferation of the intima. The perivascular sheaths present very slight cellular infiltration and Scharrlach stains show the presence of numerous fatty granules contained within cells.

*CASE 3—Pellagra in a Woman Suffering from a Manic Depressive Psychosis Death One Month after Onset with Symptoms of Central Neuritis*

*History*—A S, white female, aged 36, widow. She was a native of Scotland and but little information was available concerning her previous life. She, with her husband, adopted the religion of Dowie when in Scotland and have lived in Zion City for six or seven years. They have been in fair circumstances and succeeded in purchasing a home. In 1908 when the husband was ill the patient had an attack of excitement of manic like character lasting a few weeks. Her husband died about the end of 1908 and she apparently had an attack of depression lasting about one month, but was able to perform her housework. At the end of June, 1910, she again became restless and excited, with heightened mood. When admitted to the Elgin State Hospital July 21, 1910, she presented no evidences of somatic disease but was exalted. Her thoughts and acts were strongly colored by her religious views, with some self appreciation and she was somewhat restless. In October she became more excited, singing and dancing, interfering with others, in all this giving explanations on the basis of her religious exaltation.

A pellagrous eruption with emaciation and diarrhea were noted in May, 1911, and she died June 20, 1911, after a period in which muscular rigidity with jactatoid movements with diarrhea were noted.

The autopsy was performed by Dr. H. Smith about 24 hours after death. Unfortunately no record of the gross findings is available.

#### MICROSCOPIC EXAMINATION

*Liver* The liver shows no definite increase of fibrous tissue either in the capsule or interlobular septa. The vessels and intralobular capillaries are engorged, the latter especially in the region of the central veins. Numerous small extravasations of blood are present within the lobules. Marked fatty degeneration of the liver cells at the periphery of the lobules is present and there are many islets of infiltration with small round cells of low grade of intensity in the interlobular septa.

*Kidneys* The capsules are thickened and fibrous tissue is increased around the vessels, between the lobules and in Bowman's capsules. The vessels are engorged and there are small hemorrhages scattered throughout, but especially in the medullary rays. The glomeruli are well stained with some increase of connective tissue nuclei and are surrounded by a widened space. The secreting tubules show some swelling of cells with diffuse staining and indistinctness of outline while many contain an albuminoid material.

*Heart* The heart muscle shows thickening of vessel walls with pigmentary changes in the muscle cells.

*Spleen* The spleen presents moderate thickening of capsule and trabeculae with here and there small hemorrhages.

*Lungs* The lungs show many alveoli filled with a homogeneous material staining very faintly with eosin which sometimes contains no cellular elements but frequently numerous red blood cells and here and there shed epithelium. There is no leukocytic infiltration to suggest pneumonia.

*Suprarenals* In the suprarenal glands the vessels of the inner layers of the cortex and of the medulla are extremely engorged with blood. The parenchyma is much degenerated and in many places the cells do not stain at all, being represented only by a granular detritus.

*Nervous System* The nervous system in this case has not yet been worked up. Sections from the cortex stain badly with the Nissl stains showing but little differentiation of the granules. Nevertheless many of the larger pyramidal cells show swelling with diffuse coloration of the nucleus which is irregular in outline.

and displaced to the periphery of the cell. These changes are also very marked in the cells of the dentate nucleus of the cerebellum. Pigmentary changes have not been observed in anything like the same degree seen in the other cases. There is a moderate increase of glia nuclei along the walls of the vessels but not elsewhere. The vessel walls show moderate increase of adventitial nuclei but no perivascular infiltration.

*CASE 4—Pellagra in a Man with Advanced Arteriosclerotic Changes and Dementia. Death Six Weeks after Onset with Central Neuritis.*

*History*—F. M., white male, blacksmith, said to have been insane since 1901 and to have had a previous attack in 1886. He was admitted to the Elgin State Hospital in 1904 at the age of 67. He then showed some loss of memory and derogatory delusions. He was depressed and cried easily, refused food and threatened suicide. His physical health was poor and he suffered from hemorrhoids. He gradually failed in strength.

Pellagrous eruption with diarrhea developed in June, 1911, which improved in July, but he became worse again July 10 and died July 16 without further acute symptoms of pellagra, but with signs of central neuritis.

*Necropsy*—At the necropsy the pellagrous pigmentation was still present and the body was much emaciated. The brain showed some atrophy of the cortex and atheroma of vessels. The lungs showed hypostatic congestion and healed tuberculosis at the right apex. The coronary vessels were sclerotic but there were no other cardiac changes. The spleen and kidneys were reported to present no changes. The liver was firmer than normal. In the large intestine were a number of circular ulcers chiefly in the transverse and descending colon. They were from  $\frac{1}{8}$  to  $\frac{1}{2}$  inch in diameter.

#### MICROSCOPIC EXAMINATION

Microscopically the principal changes are. Marked engorgement of the vessels of the liver with moderate fatty degeneration of the cells at the periphery of the lobules. The connective tissue is but little if at all increased. Small hemorrhages are present in places. The kidneys show chronic interstitial nephritis with the formation of small subcapsular cysts. Small extravasations of blood are present, especially beneath the capsule. The tubules stain poorly and many contain an albuminoid material and in places epithelial cells. The pyramids are markedly congested and many vessels show hyaline change, some being occluded. The spleen shows some increase of fibrous tissue and there are small scattered hemorrhagic areas. The arteries show some hyaline change of the intima. The intestinal ulcers extend down to the submucosa and show a moderately acute small-celled infiltration. No amebas were found. Areas of infiltration with small round-cells are also present apart from the ulcers and extend even into the musculature.

*Nervous System* In this case the picture is complicated by the marked changes which are present in the vessel walls. A small hemorrhage about 3 mm in diameter was found in the crusta of the pons and another microscopical in size in the anterior cornua in the cervical region. Both were recent and in the latter the nerve cells lying in the midst of the extravasated blood cells still stained well showing well-marked Nissl granules, so that it seemed probable the extravasations were due to post-mortem injury.

Chromatolysis is well marked in the giant pyramidal cells of the precentral region and also in the larger pyramidal cells elsewhere. The Purkinje cells in the cerebellum stain faintly and some show central chromatolysis with displacement of the nucleus. Similar changes are found in a few cells in the anterior horn of the cord and more extensively in the cells of Clarke's column.

Pigmentary changes of a fatty nature are widespread throughout the nervous system as shown by Schaulach staining and this involves not only those cells

showing chromatolysis but also the smaller and other cells showing good Nissl staining. Similar fatty granules are present in large numbers contained within cells lying in the sheaths of the vessels.

The blood-vessels show marked hyaline changes in the intima, many of the smaller vessels appearing to be almost occluded. There is also hyperplasia of the adventitial coats but no small celled infiltration of the perivascular sheaths. The glia nuclei are moderately increased both along the vessels and surrounding the nerve cells.

*CASE 5—Prolonged Attack of Pellagra with Acute Exacerbations in a Man Suffering from Chronic Alcoholism with Marked Dilapidation. Death Six Months after Onset*

*History*—E. J., white male, upholsterer, 41 years of age at time of death. He was a native of Sweden and had a brother and a sister who were feeble minded. He was a heavy drinker and was irritable and unstable. In January, 1901, at the age of 31 he was arrested for drunkenness but continued in an excited state, preaching and expressing ideas of persecution. When admitted to the Elgin State Hospital in January, 1901, he was very restless and excited but seemed in good health. He continued to be violent and quarrelsome for about six weeks and then became quieter, although still quarrelsome at intervals all through his stay in the hospital. In 1908 he had an attack of acute rheumatism and is noted at that time as being "considerably demented."

*Examination*—Pellagrous erythema on the hands was noted in May, 1911, and reported as "very fiery" on July 31, 1911. At this time he was also emaciated and much weaker but without any acute mental symptoms. The pellagrous eruption was still acute on August 15 and he also had stomatitis, salivation and diarrhea. August 31 the stools were examined for amebae with negative results and the blood is reported as showing a high color index. Diarrhea continued, with progressive exhaustion and emaciation until death October 29, at which time the eruption was still present but of purple color, with marked desquamation. Plantar reflexes were of flexor type every day for two weeks before death.

*Necropsy*—The necropsy was performed by Dr. Wittman on October 29. The body was much emaciated and the muscles generally thin and atrophic. The heart was extremely flabby but no other abnormalities were noted in it nor in the lungs. The liver was described as dark brown with very obscure markings. The kidneys showed some evidences of interstitial nephritis but no other findings of importance were detected. The intestines showed no ulceration.

*Microscopically* the only findings of importance were as follows. The liver showed moderate fatty degeneration following the outline of the lobules and there were small islets of infiltration with round cells in widely separated areas of the portal connective tissue. The capillaries were engorged especially near the central veins. The fibrous tissue was not definitely increased.

The nervous system in this case has not yet been examined.

(To be continued.)

*(Continued from second cover page.)*

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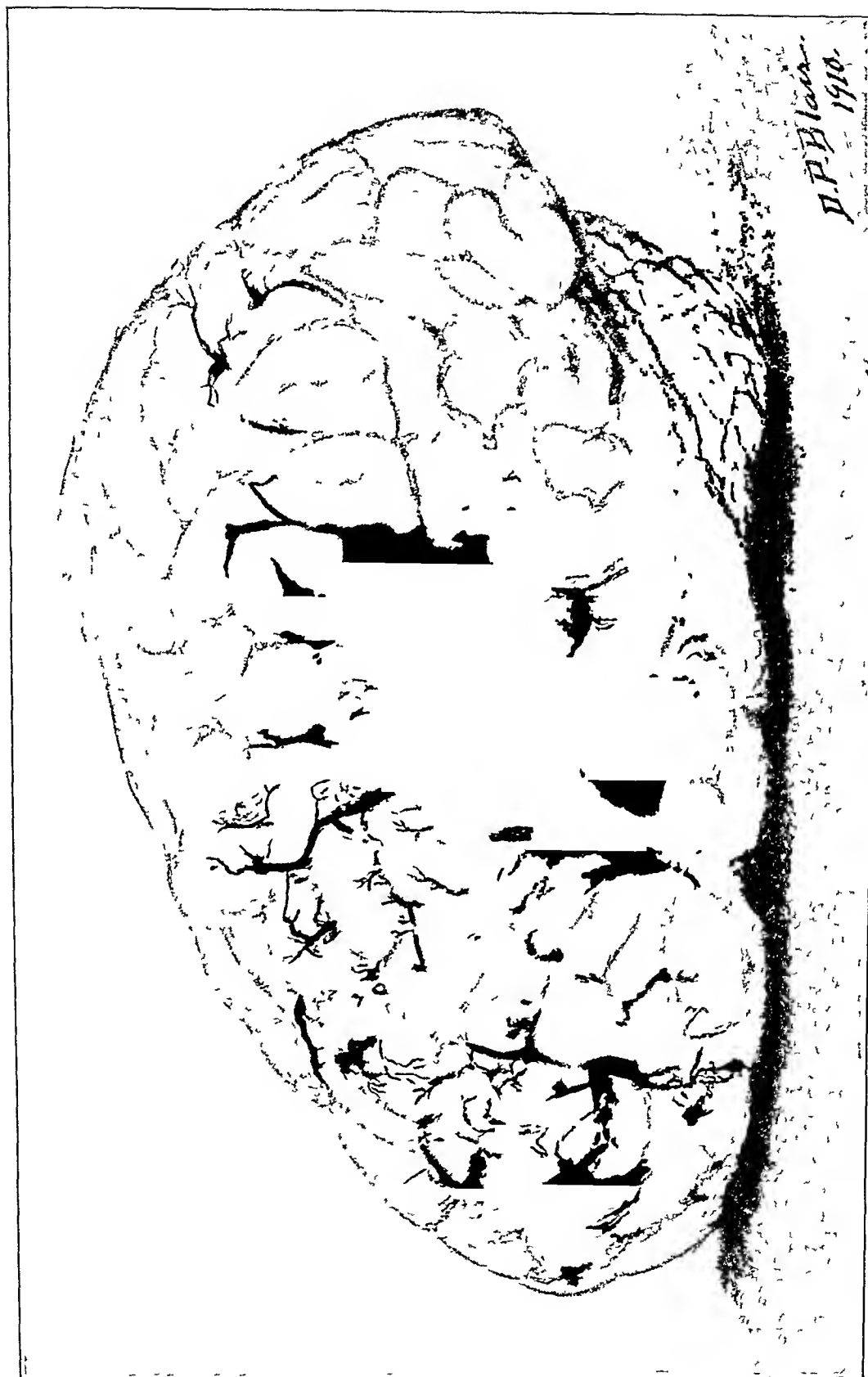


Fig 1 —Brain of Patient 1, acute hemorrhagic meningitis, from water color drawing





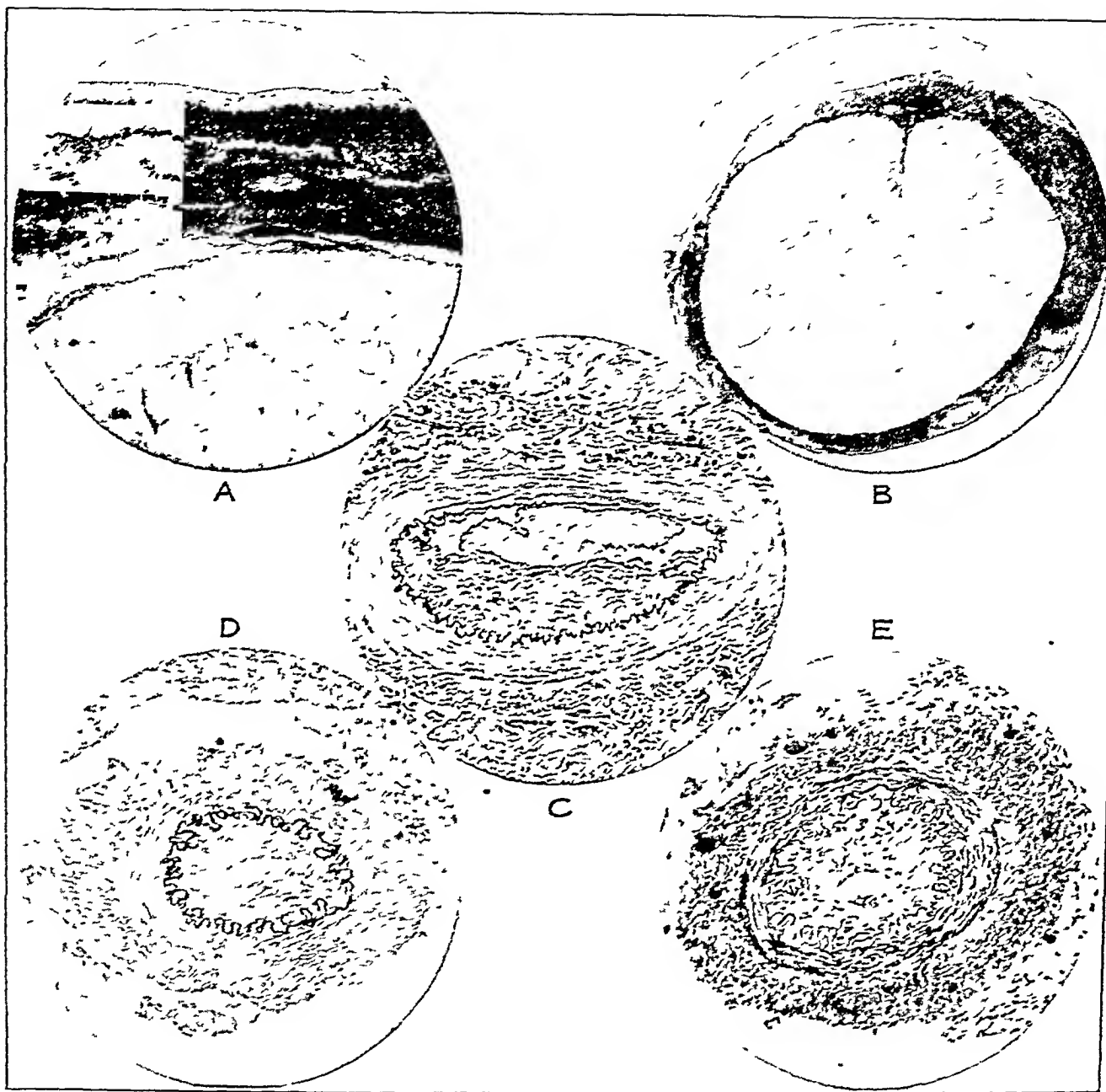


Fig 2—Pathologic changes in cerebrospinal meningitis due to *Bacillus influenzae*, from microphotographs. A, transverse section through hemorrhagic area in meninges of Case 1. B, transverse section of spinal cord Case 2. Note the marked fibrous thickening of the meninges. C, artery in pia of spinal cord near anterior commissure Case 2. Note the localized fibrous thickening internal to internal elastic membrane. D, artery in meninges of base of brain from Case 2. There is uniform fibrous thickening of the tissues internal to the internal elastic membrane. E, artery in meninges of pons from Case 2. The lumen is replaced by connective tissue in which there are small endothelial lined spaces containing red blood corpuscles and a canalized thrombus.



CASE 2—*Acute cerebrospinal meningitis and general septicemia due to Bacillus influenzae* Death from internal hydrocephalus eighty-nine days after the onset of the disease

*Clinical History*—The following clinical history was obtained from Dr Wilder Tileston, the physician in charge. The patient was a girl 5 years old. She had always been a delicate child whose digestion was easily upset. The present illness began suddenly on May 17, 1909, with fever, headache and cough. At this time the throat was very red. On the fourth day after the onset of the disease a lumbar puncture was performed and cloudy fluid under considerable pressure withdrawn. The headache was severe for the first six days, then it abated and the other symptoms of meningitis became less pronounced. Fever was present throughout the entire illness, a period of eighty-nine days. The pulse was usually increased in frequency. Beginning on the seventy-third day after the onset of the disease there were occasional attacks of transitory bradycardia, the heart-rate would fall quite suddenly (but not instantaneously) from about 140 to 70 or even 50, to rise again to its former rate or more within a few minutes. During these attacks the respirations became markedly slow and labored, and there was usually unconsciousness. The attacks were not prevented by atropin given subcutaneously in full doses. There was a progressive loss of weight from  $37\frac{3}{4}$  pounds at the beginning of the illness to  $27\frac{1}{4}$  pounds at the time of death. Nourishment was well taken, and retained up to the thirty-third day of illness, when vomiting began and was a troublesome feature from that time on. The vomiting was of the cerebral type without retching or nausea. The bowels were constipated throughout the disease. There was incontinence of urine in the last few days. Pain in the back of the neck and in the legs was complained of at times. A complete left-sided hemiplegia appeared on the forty-fourth day of illness. This persisted with some improvement until death. Ankle-clonus (now on one side, now on both) was noted at various times, both before and after the hemiplegia. Babinski's phenomenon was present only once, on the forty-eighth day, this was on the left side. Kernig's sign was present in the first days of the disease, but not very marked. During the last few weeks of life the pupils were widely dilated, but reacted to light. Strabismus was present only toward the end and was due to independent movements of the eyes, not to paralysis. The pupils were equal. Toward the close they showed frequent alterations in size, becoming greatly contracted for short periods, even after the administration of atropin.

The heart was negative except for an occasional systolic murmur at the apex and at the base.

The spleen was only once plainly palpable.

The liver was not enlarged.

There was a marked hypersecretion of mucus in the mouth.

*Urine*—During the latter part of the course of the disease there was often a heavy chalky deposit in the freshly passed urine, consisting of calcium phosphate. The urine at this time was alkaline. There was a very slight trace of albumin and an occasional cast.

*Blood*—There was a leukocytosis. May 20, 18,000, May 22, 34,000, May 27, 28,000, May 31, 20,000, June 2, 16,000. A marked pallor developed in the latter part of the illness.

*Treatment*—Early in the illness an attempt was made to influence the meningeal inflammation by the use of hexamethylenamin and of Flexner's anti-meningococcus serum. Neither of these was of real benefit. Bromids per rectum proved useful in controlling the vomiting. An autogenous vaccine was prepared from a pure culture of the influenza bacillus obtained from the cerebrospinal fluid. Three injections were made, June 10, 13 and 19, dose, 30,000,000 to 50,000,000. They seemed to have no effect on the disease. The organisms for making the vaccine were grown in large bottom flasks. In these flasks was placed sufficient blood-bouillon to make a medium 2 cm thick. By this means a large surface of the medium was in contact with the oxygen of the air.

**Bacteriological Report**—The fluid obtained from the lumbar puncture made by Dr Wentworth on the fourth day of the disease was turbid, and contained many leukocytes, mostly polynuclears, and a few delicate, Gram-negative, intracellular and extracellular bacilli. The sediment obtained from centrifugalizing this turbid fluid was smeared on the surface of agar agar plates streaked with fresh human blood. From these smears a pure culture of *Bacillus influenzae* was obtained. Two weeks after the beginning of the illness, during which time the patient ran a septic temperature, a blood culture was made. Ten cc of blood were taken from one of the veins at the elbow. Plates poured at this time averaged eight colonies of a pure culture of *Bacillus influenzae* to the plate.

The organism isolated from the cerebrospinal fluid and the circulating blood of this case corresponded in every way with the one obtained from Case 1.

**Extract from the Protocol (H 09 456)**—Dr Haythorn. Body of a fairly well developed, emaciated female child, 110 cm long. Over the entire body, with the exception of the palms of the hands and the ankles, there is a fine, dry desquamation of the skin. The axillary and inguinal lymph-glands are barely palpable. The eyes are hollow. Color is extremely pale. Lips and mucous membranes are very pale. Mouth and nose are free from discharge. Pupils are unequal, left 6 mm, right 7 mm in diameter. Muscles of the thorax and abdomen are very pale.

**Peritoneal Cavity** The surfaces are moist, smooth and glistening. The mesenteric lymph nodes are somewhat hypertrophied, the largest one measures 1.5 cm in diameter. They are firm and very pale.

**Pleural Cavities** Surfaces normal.

**Pericardial Cavity** Surfaces normal. The cavity contains 9 cc of clear, straw colored fluid. Pulmonary artery opened *in situ* contains semifluid blood.

**Heart** Weight 75 gm. Endocardium normal. Near the attachment of the aortic cusp of the mitral valve and on its ventricular surface there are two small, yellowish pin-point areas of thickening. On the aortic surface of the upper portion of the right coronary cusp there is a similar lesion. The heart muscle is uniformly pale and firm. Coronary arteries normal. Foramen ovale closed.

**Lungs** Pleural surface normal. Parenchyma is pale and crepitant throughout. Both lungs show slight edema. There are no visible or palpable areas of consolidation.

**Spleen** Weight, 35 gm. It is rather soft. The cut surface is reddish purple. Malpighian bodies prominent. Considerable blood adheres to the knife on scraping.

**Liver** Weight 642 gm. Surface smooth. Anatomical markings are fairly distinct. Bile-passages normal.

**Kidneys** Combined weight 132 gm. Capsule strips easily, leaving a smooth, pale surface. Cortex averages 6 to 8 mm in thickness and is very pale. The ureters are slightly distended in their lower thirds.

**Adrenals, Aorta, Genital Organs and Pancreas** Normal.

**Gastro Intestinal Tract** There is no evidence of disease. Peyer's patches and solitary follicles are not prominent.

**Organs of Neck** The tongue is clean and pale. Tonsils slightly hypertrophied, they show no acute exudation. Lymphatic glands of neck are not enlarged. Thyroid and larynx normal. Thymus weighs 6 gm. is pale and rather soft.

**Head** External ears are free from discharge. Scalp and calvarium are normal. The great longitudinal sinus contains very little blood. Dural vessels are greatly flattened. The brain is exceedingly tense and bulges through the incised dura. Pial vessels are moderately injected. The convolutions of the hemispheres are broad and flat, and the sulci are shallow. There are a number of irregularly distributed, fairly sharply outlined, pale, brownish-yellow areas of thickening of the pia. These areas are larger along the course of the large blood vessels. The largest areas of thickening are situated over the precentral convolutions and along the fissures of Sylvius. The anatomical markings of the base of the brain pons and medulla oblongata are obscured by a grayish tinge,

fibrous thickening of the meninges, which binds the pia to the overlying tissue. This marked thickening of the meninges of the base of the brain begins anteriorly in the region of the optic commissure, extends backward along the crura over the infundibulum and corpora albicantia to the pons, surrounds the medulla and extends upward over the anterior portion of the cerebellum. The cerebellar hemispheres are firmly bound together by dense fibrous connective tissue. The ventricles are distended, the lateral ventricles contain 250 cc of clear, straw-colored fluid which is under great pressure. When this fluid is drained away through an opening made at the base of the brain, the dome of the cerebrum is flattened and the ventricles are collapsed. The circumference of the left lateral ventricle in its mid-portion is 12 cm. The average thickness of the overlying brain substance is 1.5 cm.

**Spinal Cord** The pia of the spinal cord is greatly thickened, most markedly on one side. It is tough and of a yellowish-white color. This pial thickening is most pronounced in the cervical region, extends a short distance along the posterior nerve-roots, and thins out in the lower portion of the cord. The sinuses at the base of the brain contain a small amount of post-mortem clot.

**Middle Ears** Normal.

**Anatomical Diagnosis**—Chronic cerebrospinal meningitis, internal hydrocephalus, chronic endocarditis—mitral and aortic valves.

**Bacteriological Report**—Cultures were made at the autopsy on media most favorable to the growth of *Bacillus influenzae*. These cultures were taken from the heart's blood, liver, kidney and spleen, meninges of the brain and cord, several areas in the cerebral tissue, and from the cerebrospinal fluid. They were all negative for the influenza bacillus.

**Histological Report**—Tissue for examination was fixed in Zenker's fluid, 10 per cent dilution of liquor formaldehydi and alcohol 95 per cent, and stained by means of eosin and methylene-blue, Gram-Weigert and Mallory's connective tissue stain and Mallory's phosphotungstic acid hematoxylin, fat stain and Verhoeff's elastic tissue stain.

**Lungs** There are a few very small areas of acute inflammatory reaction. No organisms resembling *Bacillus influenzae* are present.

**Kidneys, Liver and Heart** These show a moderate amount of intracellular fat. The remaining organs are unimportant.

**Spinal Cord** Histologically the meninges of the spinal cord are greatly thickened by connective tissue which is infiltrated with lymphocytes. This thickening is most marked throughout one side. Peripherally the meninges of the cord show numerous newly formed blood-vessels, a fairly active process of organization. The infiltrating cells are plasma cells and large and small lymphocytes. Besides the thickening and cellular infiltration of the meninges of the cord there are lesions of certain of the pial blood-vessels. Some of the larger arteries show focal or diffuse areas of thickening of the intima. This intimal thickening is most marked in the arteries that run along the anterior commissure and is due to a dense connective tissue internal to the elastic membrane. The arteries showing these lesions have their lumina somewhat infringed on but none examined showed complete occlusion.

**Cerebrum** The thickened areas of the meninges of the brain show the same general picture as is seen in the thickened areas in the pia of the cord. The blood-vessels in these areas of thickening show lesions similar to those in the cord. One of the small arteries at the left side of the base of the brain is almost obliterated by fibrous tissue internal to the internal elastic membrane. The lumen of one of the smaller arteries in the pia covering the pons is replaced by dense fibrous tissue in which there are several small openings lined with endothelial cells. Some of these openings are filled with red blood-corpuscles. None of the sections examined showed lesions of the blood-vessels of the brain substance itself.

The connective tissue thickening in the meninges of the cord and brain is due to the organization of an exudate. The lesions in the blood-vessels most

probably have resulted from one of three changes first, they may be organized thrombi which have been covered by the endothelial cells lining the blood-vessels, second, they may have resulted from a fibrosis following degenerations of the type seen in arteriosclerotic processes, third, some of them may be due to changes following exudation beneath the endothelial lining of the blood-vessels. Of the three causes suggested as an explanation of the pathological changes in the blood-vessels, numbers one and three are the most probable. The lesion in the artery whose lumen has been replaced by connective tissue in which there are small spaces lined with endothelial cells and filled with red blood corpuscles, can most easily be explained as the result of the canalization of a thrombus. Thrombi in the vessels of the central nervous system have been described in influenzal meningitis. The organization of a small thrombus or a subendothelial exudate would explain the lesion in those vessels that show increase in connective tissue which is limited to a part of the vessel wall. Subendothelial exudates occur in meningitis due to certain organisms and in the smaller blood vessels of animals that have been injected with *Bacillus mallei* or its toxin.

The important points in this case are the cultivation of the influenza bacillus from the circulating blood and the cerebrospinal fluid, the prolonged course of the illness, the development of internal hydrocephalus and hemiplegia. The hydrocephalus may have resulted from obstruction of the foramen of Magendie following the organization of meningeal or ependymal exudate. To the hydrocephalus may be attributed the pupillary signs, the attacks of unconsciousness, with slowing of the pulse and respiration, and vomiting.

The acute meningitis in this case probably followed involvement of the upper air passages, as the earliest signs of infection were noted in this location. It could not be determined whether or not the intracranial infection occurred as a direct extension from the nasopharynx or its accessory sinuses, the middle ears, mastoid cells, or by way of the circulation. There was neither clinical nor post-mortem evidence of infection of the middle ears, mastoid cells, antra of Highmore or basal sinuses.

The important points illustrated by these two cases are the following:

1 The influenza bacillus may produce a meningitis in which there are extensive intrapial hemorrhages.

2 In influenzal meningitis there may be an acute inflammatory reaction about the blood-vessels in the brain substance. These inflammatory changes may be related to some of the permanent lesions of the central nervous system following some of the acute illnesses associated with cerebral symptoms.

3 Bacteremia may develop in the course of influenza.

4 The organization of an acute exudate in influenzal meningitis may, by interfering with the normal circulation of the cerebrospinal fluid, lead to internal hydrocephalus.

5 In chronic meningitis following acute influenzal meningitis the arteries of the meninges may show varying degrees of increase in connective tissue internal to the internal elastic membrane.

6 Influenzal meningitis may be followed by paralysis of varying extent.

## SOME OBSERVATIONS ON HEART-BLOCK \*

JAMES G VAN ZWALUWENBURG M D

ANN ARBOR, MICH

The subject of heart-block has held a prominent position in recent medical literature. Certain features of the following cases of auricular-ventricular block appeal to me as deserving of record and discussion. They are taken from the records of the University Hospital and presented in this form on the recommendation of Dr A W Hewlett, to whom I am indebted for many valuable suggestions.

*CASE 1—History*—B E M, 28, student, was admitted May 20, 1909, complaining of dizziness and dyspnea on exertion. His family history and habits were good. Two years previously he suffered from a very severe tonsillitis followed by acute rheumatism. During the second week of his illness the heart-rate increased out of proportion to his illness, rising to 170 on sitting up. There was no pain but excessive nervousness and a small goiter developed. He improved on thyroidectin after seven months in bed, the pulse-rate dropping to 80-90 at the end of that time. This rate has persisted since then though he has had occasional attacks of "heart hurry." Two weeks previous to admission he had tonsillitis with little fever, and a week later the tachycardia returned with dizziness and dyspnea. After two days the heart-rate fell to 50, rose gradually to 90 and then suddenly to 160.

*Examination*—Color good. Skin moist and warm. A small soft goiter, no thrill, no murmur, no eye signs. Slight lagging over the right upper thorax, auscultation of lungs negative. Some evidence of cardiac enlargement, a faint diastolic murmur noted in the pulmonary area. Radial pulse soft, large, and quick, with no irregularity.

*Course of Disease*—Within a few hours after admission a partial heart-block was noticed with variable ratio between the auricular and ventricular rates, at one time a 2-1 rhythm persisted for a short time, but usually the ratio was 3-2. The *a-c* intervals in seconds were estimated as follows: 0.27-0.36-0.44-block, 0.26-0.36-0.40-block, etc. The shortest measured interval was 0.25 second and the longest 0.57 second. Following 1/50 gr atropin the pulse became regular with an *a-c* interval of 0.27-0.30 second. Twenty minutes later there were five intermissions in one minute and five hours later the former arrhythmia had been resumed. The following morning 1/100 gr atropin was given and the pulse became and remained regular.

Oct 25, 1909. All symptoms had disappeared, the orthodiagram showed a reduction of 9 per cent in the area of the heart shadow and there was no murmur.

Oct 19, 1910. The patient returned with an afternoon temperature, a chronic cough and definite signs on the left upper chest behind. No tubercle bacilli were found. He now complained of intermissions in the pulse associated with a thump in the pericardiac region causing a cough. These were due to ventricular extrasystoles. The pulse rate ranged from 80 to 100 per minute.

The heart-block in this case may be ascribed either to nervous influences or to the infection, both of which are commonly recognized as

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\*From the Department of Internal Medicine, University of Michigan

causes of dissociation. It is to be noted, however, that the irregularity followed a period of rapid pulse-rate which in itself may lead to partial heart-block as has been shown by Erlanger and Hirschfelder.<sup>1</sup>

The prompt improvement under the administration of atropin is convincing proof of the presence of some vagus effect. The action of the drug was not the usual one, however, as may be seen from the following

Date	Time	Auricular Rate	Rhythm
5/20/09	At entrance	110	2 1 and 3-2
5/21/09	Before atropin	110	3 2
5/21/09	2 hrs after atropin	95	Regular or occasional block
5/21/09	5 hrs after atropin	90	4-3
5/22/09		82	Occasional block
5/22/09		72	Regular

The atropin produced a disappearance of the block with an improvement in the transmission time but the auricular rate has fallen rather than increased as is the usual effect. A similar experience in a case of partial block is recorded by Griffin and Cohn.<sup>2</sup>

**CASE 2—History**—S. M. B., April 12, 1910, was admitted to the otological clinic for the radical mastoid operation. Except for chronic alcoholism his previous history was negative. On April 18, operation was deferred because of delirium tremens.

**Operation**—On May 9 patient was operated on under ether anesthesia. The lateral sinus was exposed, also the dura over the roof of the antium low down.

**Course of Disease**—The temperature fell to normal on the following day. On May 15 the patient complained of sharp darting pains in the head and over the face. The temperature rose to 102.2 and there was some evidence of infection in the wound. An irregular temperature persisted until the 24th. On the 23d the pulse-rate fell to 48 in the presence of a temperature of 101.2 F and for four days the rate never rose above 56. A neurological examination on this date showed nothing. On May 26 it was noted that the pulse was irregular as well as infrequent and a tracing was taken showing an incomplete block with a 3-2 and 4-3 rhythm. The range of the *a-c* intervals was 0.27-0.42 second.

Before the action of atropin or mechanical stimulation of the vagus could be tried the pulse became regular and remained so thereafter. Tracings taken the following day were normal with an average *a-c* interval of about 0.27 second. During the several months' residence in the hospital the arrhythmia was never again observed.

The arrhythmia in this case, as in the preceding one, was probably due to vagus influence plus infection. In the absence of neurological evidence we are scarcely justified in assuming a local meningitis, or irritation of the vagus nerve. Unfortunately we were unable to apply the atropin test before recovery although we were saved, thereby, from a

<sup>1</sup> Erlanger and Hirschfelder. Physiology of Heart-Block in Mammals, *Am Jour Physiol*, 1906, xv, 153.

<sup>2</sup> Griffith and Conn. Remarks on the Study of a Case Showing a Greatly Lengthened *a-c* Interval with Attacks of Partial and of Complete Heart-Block, with an Investigation of the Underlying Pathological Conditions. *Quart Jour Med*, 1910, iii, 126.



probable misinterpretation of our results as *propter hoc* instead of *post hoc* in case it had resulted favorably

CASE 3 —*History*—March 13, 1909, a musician, aged 54, came complaining of shortness of breath and edema. He had all the features of a chronic interstitial nephritis with cardiac failure, relative murmurs, enlarged liver, chronic emphysema and a systolic pressure of 210 mm Hg. As his condition was urgent, he was given 1 mg of strophanthin and its action controlled by plethysmographic records. No irregularity was noted during the short period preceding administration of the drug. Within two or three minutes after this the tracings became slow and markedly irregular, enough to give rise to considerable alarm on the part of the attendants. The patient was not aware of any change in his condition.

At 5 30 (an hour later) phlebograms were taken. At the time these could not be interpreted, but they were later and in the light of clearer tracings recognized as those of partial block with a 3 to 1 rhythm, by the 17th tracings were obtained which were recognized as those of a partial heart-block. On the 20th 1/100 gr atropin was given without recognizable influence on the arrhythmia. Mechanical and thermic stimuli produced no definite change. On March 22 digitalis was resumed in doses of 80 drops of the tincture per day for five days. The block still continued to come and go. It did not seem to be aggravated by digitalis.

The *a-c* interval was carefully estimated in a considerable number of tracings. The following are the averages for different rhythms.

During regular rhythm	17-22 sec average 20
Occasional block	13-22 up to 35-block
3-2 rhythm	13-24 block
2-1 rhythm	17-block

It is worthy of note that the shortest *a-c* interval (following a block) is considerably shorter than the usually accepted normal interval and that the interval just preceding the blocked stimulus shows comparatively little increase over the normal.

James MacKenzie<sup>3</sup> first reported a partial heart-block after giving members of the digitalis group, and this was later confirmed by numerous observers. We believe this case unique in the suddenness of the onset.

The production of partial heart-block by digitalis is usually ascribed to the stimulation of the vagus inhibitory mechanism, especially where an abnormally long *a-c* interval previously existed (MacKenzie<sup>4</sup>). Cushny<sup>5</sup> suggests that direct action on the conductivity of the bundle of His may be an important factor since in animals a complete block induced by digitalis is often refractory to large doses of atropin. In partial block the vagus action in man has been shown to persist by the fact that block may be induced in some cases by vagus compression or even swal-

3 MacKenzie Diseases of the Heart, London, 1908, p. 180

4 MacKenzie New Methods of Studying the Heart, Brit Med Jour, 1905, 11, 587, 702, 759, Clinical Methods of Recognizing Heart-Block, Brit Med Jour, 1906, 11, 1107

5 Cushny The Therapeutics of Digitalis and Its Allies, Am Jour Med Sc, 1911, cxii, 469

lowing Rihl<sup>6</sup> and H E Herring<sup>7</sup> state that in all previously reported cases of digitalis block the auricular rate has been increased during the irregularity. The case of A W Hewlett<sup>8</sup> seems to be the only exception to this rule.

This case under discussion showed this increase in auricular rate in remarkable degree as may be seen from the following table:

Time	Auric rate	Ventric rate	Rhythm
At entrance—			
3/13/09	125	125	Regular
After strophanthin—			
3/13/09	162	82	2:1
3/15/09	98	98	Regular
3/17/09	120	80	3:2
3/18/09	116	82-116	Variable
3/26/09	110	110	Regular
3/27/09	120	280	3:2

It will be observed that we have here the reverse of the paradoxical action of atropin recorded in our first case, in that a drug which usually slows the auricle by vagus inhibition caused an increased auricular rate. Moreover, the degree of the block varies with the auricular rate. Nor does the exhibition of atropin alter the picture to any considerable degree. It has been suggested that the mechanical effect of the auricular stasis stimulates the sinus to more frequent stimulus production. Thus by its tendency to aggravate the block establishes a vicious circle which may be interrupted either by improving conduction or slowing the auricle.

From the reports of Bachman<sup>9</sup> it appears that, in complete block, conditions are very different, since atropin in such cases increased the auricular without influencing the ventricular rate and the digitalis bodies slowed the auricular but increased the ventricular rate, that is, the usual vagus effect is obtained with both atropin and digitalis, while the increased ventricular rate with the latter is ascribed to direct muscular action.

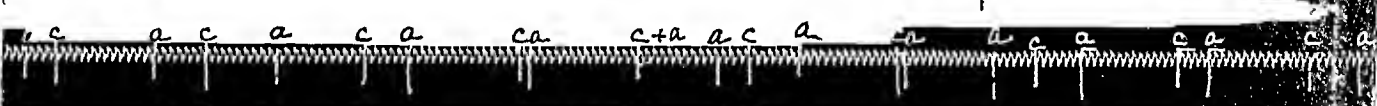
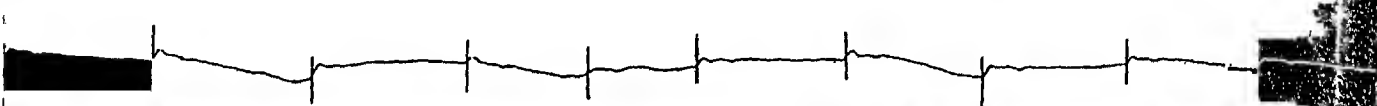
CASE 4—*History*—A B, 72, colored, came to the hospital April 29, 1910, complaining of shortness of breath and weakness. His first illness began seventeen years ago with symptoms of a urethritis and cystitis. Three years ago, a retention developed and suprapubic drainage for eight weeks was necessary. About a month previous to his entrance to the hospital, he suddenly became unconscious as he was sitting quietly. He fell to the floor and "believes he was paralyzed." Since then he had been short of breath, had coughed and grown weaker so that finally he went to bed. There had been some pain below the left clavicle on deep breathing. The left side had been tapped and considerable fluid drawn off, the patient did not know how much.

6 Rihl. Klinischer Beitrag zur Kenntnis der Ueberleitungsstörungen von der Bildungsstätte der Ursprungsreize zum Vorhof, Deutsch. Arch. f. klin. Med., 1908, xciv, 286.

7 H E Herring. Verhandl. d. Congr. f. inn. Medizin, 23. Congr., 1905, p. 153.

8 Hewlett. Digitalis Heart-Block, Jour. Am. Med. Assn., 1907, xlviii, 47.

9 Bachman. Sphygmographic Study of Complete Heart-Block, THE ARCHIVES OF INTERNAL MED., 1909, iv, 238.



.67	.68	.67	61	57	42	42	56	57	48	74	81
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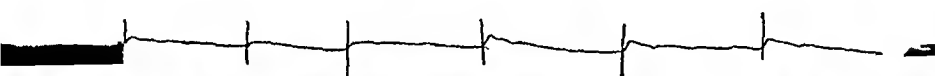
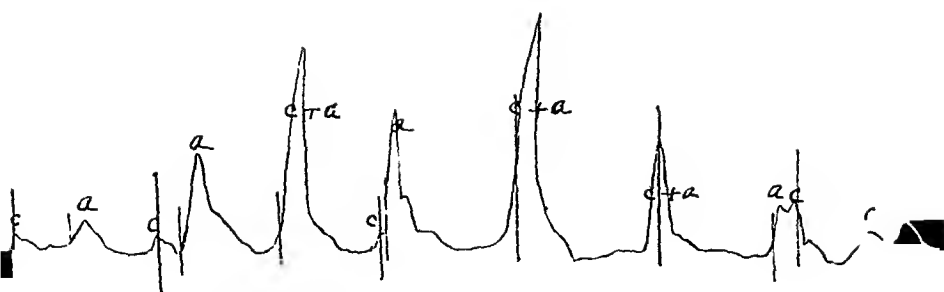
81	80	80	62	58	78	79	79	79	72		
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81	80	80	62	58	78	79	79	79	72		
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81	80	80	62	58	78	79	79	79	72		
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81	80	80	62	58	78	79	79	79	72		
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but with fairly close relations between the *aa* and *cc* intervals when not complicated by a block Th



79	60	54	62	72	80	66	
47		58	72			70	

31	13		00				
78	67	58	76	80	81		

60	50	62	72	80	66		
47	54	58	72	80	81		
78	67	58	76	80	81		

79	60	54	62	72	80	66	
47	54	58	72	80	81		
78	67	58	76	80	81		

best shown in the later portion or the hypothetical diagrams

*Examination*—On entrance the bedside chart showed a temperature with a maximum of 100.4 F, pulse 92, respirations 22. The patient was orthopneic with marked Cheyne-Stokes breathing, cyanosis of the mucous membranes and full throbbing vessels. There were signs of fluid in the left pleural cavity, as high as the third rib in front with numerous rales over the remainder of both lung areas. The cardiac impulse was diffuse and might be seen as high as the manubrium and on the right side. The apex-beat could not be located by sight or touch. A slight diastolic shock was noted in the second left intercostal space. The left border of the heart dulness was lost in the dulness of the fluid. The right border was 6 cm to right of the median line. Both sounds were distant at the apex and without murmurs. The aortic second was accentuated, also the pulmonic second. The radial was thickened, large, full and incompressible. Systolic blood-pressure was 195 mm Hg. The liver was enlarged, firm but not tender or pulsating. There was no edema. Deep reflexes were normal. The urine showed fairly large amount of albumin, and microscopic pus. Red blood-cells numbered 4,810,000, white blood-cells 4,450, and hemoglobin was 80 per cent.

*Course of Disease*—Three days later a diagnostic puncture furnished a light yellow fluid, specific gravity 1.017 with 750 white blood cells per cmm, nearly all of which were lymphocytes, 40 per cent showing badly degenerating nuclei. The pleural fluid gradually decreased under depleting measures so that on the thirteenth day in the hospital the apex could be located in the fifth left intercostal space within the nipple line. The following extract is taken from a note made by Dr Hewlett on that day: "There is a very unusual variation in the quality of the first sound, most marked at the apex but heard over other parts of the heart. At times it is loud and ringing, at others soft and muffled so that it can hardly be heard. This does not seem to depend on respiratory movements.

The heart is quite irregular with no relation between this and respiration. The irregularity is much less noticeable at the wrist and might easily be overlooked."

On the seventeenth day (May 5, 1910) a retention developed calling for catheterization. The urine became scanty and highly albuminous and the patient died in uremia on the twenty-eighth day (May 26, 1910).

Autopsy was refused.

The numerous polygrams from this patient fell into four classes according to the time of rhythm.

Figure 1 represents the most frequent and persistent type and is perfectly regular. It is part of a long record which remained uniform for eight minutes. In this tracing the average *c-c* interval calculated from the carotid pulse measures 0.70 second with a minimum of 0.68 second and a maximum of 0.71 second. The phlebogram shows a positive venous pulse, but the true character of the systolic elevation is not apparent until the irregular period at the end of eight minutes is studied.

This is shown in Figure 2, and represents the second type of arrhythmia, viz, with the ventricles irregular and the auricles regular. The *a* and *c* waves are here easily recognized and from the portion of the tracing immediately preceding and following this irregular stage the relation of the *a* and *c* wave is easily made out. Throughout the records the *c* wave of the phlebogram slightly precedes the systolic rise on the carotid, i.e., the venous *c* wave is "protosystolic" (Bachman<sup>10</sup>). The irregularity cov-

10 Bachman Interpretation of the Venous Pulse, Am Jour Med Sc, 1908, LVIII, 674

ers the period between the points marked *m* and *n*, including four ventricular and five auricular systoles. It will be noted that there is little change in the *a-a* intervals. The value of the third *a-a* interval is estimated at 0.66 second, although the summation of the *a* and *v* waves at this point makes its determination somewhat problematic. On the other hand the *c-c* intervals have suddenly increased from an average of 0.70 second to 0.96, 0.92 and 0.90 second respectively. These values show a difference which is very near the limit of error and do not exceed the difference between successive values elsewhere in the tracing.

Figure 3 is a reproduction of a tracing taken while the pulse-rate was considerably elevated. It represents the third type of tracing with the auricles irregular and the ventricles regular. The *c-c* interval is regular with an average of about 0.58 second corresponding to a ventricular rate of about 104. The phlebogram shows a striking alternation of high and low waves. The former occur where the period of auricular systole overlaps that of ventricular systole. Where this does not occur the excursion is comparatively slight and the waves well differentiated. In the twenty-three seconds represented in the tracing there are three more auricular than ventricular waves representing an auricular rate of about 113 as against a ventricular of 104. The *a-a* interval varies considerably (from 0.42 to 0.65). The same condition is more convincingly shown in Figure 4, taken on the previous day, when the pulse-rate was less elevated. The average *c-c* interval is 0.75 second, corresponding to a rate of eighty per minute. The average *a-a* interval is 0.68 second, equivalent to ninety per minute. Moreover, the *a-a* intervals vary from 0.52 to 0.78 without any corresponding variation in the *c-c* intervals.

Figure 5 is an example of the fourth type of tracing, in which the auricle and ventricle are both irregular. The patient had received 60 drops of tincture of digitalis during the previous thirty hours but similar tracings were obtained several days previously. Next to the regular type of tracing illustrated in Figure 1, it is the most frequent form. It will be noted that the *c-c* intervals vary from 0.61 to 0.81 second in a rhythmical manner independent of the respiratory rhythm while the *a-a* interval is subject to sudden and irregular changes.

Except in tracings of the first type it is apparent that we are dealing with some form of heart-block. Whether the block is complete or partial is not so evident.

In the light of subsequent tracings, it is easily seen that in Figure 1 we have a regular pulse with an unusually long *a-c* interval as a result of which the *a* wave falls on the *c* wave of the next preceding ventricular contraction. The transition is well marked in Figure 2, and allows of no other interpretation.

Tracings showing a similar incidence of the *a* waves on the *c* waves have been reproduced by Wenckebach,<sup>11</sup> Griffith and Cohn,<sup>2</sup> Thayer and Peabody<sup>12</sup> and others. Wenckebach<sup>13</sup> has applied the name of *Voithof-Pfropfung* to this condition and finds the cause in the relation of the *a-c* to the *a-a* intervals. Thus it occurs whenever these become approximately equal whether from lengthening of the former in disturbed conductivity or abbreviation of the latter in tachycardia. Similar phenomena occur throughout the tracings from this patient.

It is possible in any case of auricular-ventricular dissociation in which the auricular exceeds the ventricular rate to construct a diagram showing the time relations of auricles and ventricles and by connecting judiciously selected points by slanting lines to assume the block of a number of auricular impulses equal to the difference between the two rates. Such a diagram cannot be taken as evidence of the transmission of any of the auricular stimuli to the ventricle since the relationship may be purely accidental. In a partial block we expect to find (a) the blocked impulse represented by a long interval in the carotid pulse, (b) the *a-c* interval increasing by a progressively smaller increment up to the following block, and (c) the "allorhythmia" of Wenckebach in the radial in which the first *c-c* interval following the block is the longest of the transmitted intervals.

Applying these criteria to the diagram in Figure 2, we find the block represented by a *c-c* interval of 0.96 second, which is within reasonable errors the same as the following intervals, the increase in the *a-c* intervals following are 0.20 and 0.24 respectively (increasing increments), and the second long beat is approximately equal to the first and third. Two interpretations are here possible, viz., the block is partial and the *c-c* intervals are so nearly equal by the accidental increase of the *a-c* interval, just sufficient to produce this, or the block is complete and the ventricles have taken an automatic regular rhythm.

A somewhat similar tracing showing only two long radial pulse periods was reproduced by Joachim<sup>14</sup> and interpreted by the former hypothesis. Estimated from these tracings as reproduced the longest *a-c* interval is about one second while the preceding intervals are not much above the normal. Both Wenckebach<sup>11</sup> and Rühl<sup>6</sup> have questioned this interpretation and published similar instances as showing automatic ventricular contraction.

11 Wenckebach. Beiträge zur Kenntnis der menschlichen Herztätigkeit, Arch f Anat u Physiol, 1908, Abtlg., Supplement Band 53.

12 Thayer and Peabody. A Study of Two Cases of Adams-Stokes Syndrome with Heart-Block, THE ARCHIVES INT MED, 1911, vii, 289.

13 Wenckebach. Ueber eine kritische Frequenz des Herzen bei paroxysmaler Tachycardie, Deutsch Arch f klin Med, 1910, ci, 402.

14 Joachim. Ein atypischer Fall von Störung der Reizleitung in Herzmuskel, Berl klin Wchnschr, 1908, xlv, 911.

Gibson and Cohn<sup>2</sup> report a somewhat similar case with alternative diagnosis, selecting as most probable the one assuming an *a-c* interval exceeding one second. Thayer and Peabody's<sup>12</sup> tracings are somewhat similar and are interpreted as due to automatic ventricular contraction.

In the case under consideration the indicated *a-c* interval of 0.90 second is not greater than occurs elsewhere where no other interpretation is possible, while an automatic rate of sixty-six per minute, which is equivalent to the rate of the long periods, is exceptionally high except under toxic doses of digitalis (Cushny<sup>6</sup>). The tracings of Hewlett and Barringer<sup>15</sup> are interpreted as such effects.

The third type of tracings with irregular auricle and apparently regular ventricle is still more involved. In Figure 3, there is absolutely no indication in the carotid of the location of the blocked stimuli. The *a-c* interval fluctuates although tending to increase to an uncertain limit. Where an *a-c* interval is shorter, however, than its predecessor it is found to correspond to a longer *a-a* interval, possibly because the His bundle has had the longer time to recover. The contrary is also found. It seems improbable that these two factors should be so perfectly balanced as to leave no evidence of the auricular irregularity in the carotid tracing. The difficulty of recognizing the blocked auricular impulse is not removed by a study of the values of the *a-c* intervals since such short intervals as 0.08 second shown in the diagram are quite incompatible with the interval of 0.61 second during the regular periods (see Fig. 1). The inference is that the ventricle in such cases responds to the stimulus of the next preceding beat. But where the series of *a-c* readings is 0.08, 0.08, 0.16, 0.18, 0.20, 0.28, 0.34, 0.38, as occurs in the latter portion of Figure 3, there is no good indication for selecting any stimulus as the one that is blocked. The alternative of a complete block with an independent regular rhythm is very attractive in this connection, except for the unusually high frequency of the automatic ventricular rates of 113 per minute which it implies. With the exception of the case reported by Hewlett and Barringer<sup>15</sup> the rate of sixty-six in a case of complete heart-block reported by Windle<sup>16</sup> is the highest which has come to our notice.

In connection with a tracing showing similar rhythmical variations in the size of the auricular wave, Wenckebach<sup>11</sup> has observed a variation in the intensity and quality of the heart sounds in every way similar to that noted by Dr. Hewlett in the history and ascribes the *Vorhof-Pfropfung* above described as the cause.

In Figure 5 the difficulty of identifying the blocked stimulus is nearly as great. There is, however, an added irregularity of the carotid which reflects more or less perfectly the irregularity of the auricle plus

<sup>15</sup> Hewlett and Barringer. Effect of Digitalis on the Ventricular Rate in Man, *THE ARCHIVES INT. MED.*, 1910, v, 1.

<sup>16</sup> Windle. Permanent Complete Heart-Block, *Heart*, 1910, 11, 102.



an occasional block Two alternative diagrams are given as plausible interpretations of this tracing although others are possible The relationship between the two rhythms is too close to allow of interpretation as complete block—it would be inconceivable that two independent rhythms should show similar fluctuations for any considerable length of time The long periods of regular rhythm are also incompatible with an independent ventricular rhythm

#### SUMMARY

1 Two cases of partial heart-block due to vagus stimulation or to acute infections or to a combination of these

2 One case of partial block following the injection of 0.001 gm of strophanthin

3 One case of partial block apparently cured by the use of atropin Two cases in which such injections produced no notable effect on the block

4 When the block followed strophanthin the auricular rate was increased and when the block disappeared after atropin the auricular rate was lessened

5 The last case showed partial block with the following peculiarities

A Long periods of regular rhythm during which the auricles contracted during ventricular systole In such cases the ventricles responded to the stimuli coming from the previous auricular contractions, the *a-c* interval being about 0.60 second

B Repeated *a-c* intervals of more than 0.80 second

C Auricular irregularity with such relations between the *a-c* intervals and the *a-c* increments due to fatigue that the ventricles showed no evidence of the auricular irregularity

319 Glen Avenue

# FRACTURE OF CERVICAL VERTEBRÆ, RESULTING IN HYPOTONIA AND HYPOTHERMIA\*

HAVEN EMERSON, M D  
NEW YORK

*The Injury*—On the evening of Jan 28, 1911, a man was seen to fall from a subway station platform to the tracks, about 4 feet below, on his back. He was lifted to a seat on the platform and a policeman who was notified called an ambulance. On the arrival of the ambulance surgeon, about fifteen minutes later, the man was found to be confused, and to be weak but not powerless in his legs. The knee-jerks were present and his arms and trunk showed ample strength. He could not walk and there was a smell of liquor on his breath, so he was taken to the police station, charged with intoxication.

The next morning the officer in charge found the man unable to stand, though less confused and able to give a fair account of himself. The ambulance surgeon was called again and found the reflexes at the knees weaker but still present, and an increasing disability in the legs. The man could use his arms and trunk to some extent. He was brought to the prison ward at Bellevue Hospital, charged with intoxication but with a diagnosis of transverse myelitis or possible fracture or dislocation of a cervical vertebra.

On admission on January 29, the patient was semi-conscious, roused later, and became somewhat noisy. His eyes were stupid and staring. He gave a connected story of himself but had forgotten having gone down into the subway station. He remembered walking along the street and feeling dizzy, and then coming to himself in the station house.

*History*—He gave a family history as follows, and it was corroborated by his wife and his employer.

Father is living and well, occasionally subject to dizzy spells. Mother died at 28 of tuberculosis. There was one brother, who died at 44 of softening of the brain. There has been tuberculosis among aunts and uncles.

He says he has never been sick except for an attack of gonorrhea fifteen years ago, has always been in vigorous health and a hard worker, never took medicine or was under a doctor's care. He is a porter by occupation, a negro, 38 years old, married and has no children. He is accustomed to use beer moderately and gin occasionally in his home or at the house of friends. He is not a user of tobacco. Uses tea and coffee in moderation.

*Examination* (January 30)—An unusually well nourished and well developed negro, with a well shaped head and intelligent face. Nothing abnormal was found, except a distended bladder, evidence of injury at the back of the neck and extensive motor and sensory paralysis. There was a temperature of 97.8, pulse 58, respiration of 20 in the minute, pulse small and easily compressible. There was incontinence of feces and retention of urine, no difficulty in swallowing, breathing of diaphragmatic type.

There was no interference with any of the special sense organs, but there was a persistent and equal contraction of the pupils, so extreme that but slight response to light could be elicited.

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\*Report was read at the meeting of the American Society for Clinical Investigation, May 8, 1911.

\*This case is reported from my term of service as physician to the alcoholic and prison wards of Bellevue Hospital, and the clinical observations were corroborated by Dr V H Norrie, visiting physician to Bellevue Hospital.

From the region of the fifth to the seventh cervical spines there was moderate tenderness with acute pain on pressure where the sixth spine should have been felt. Owing to the heavy musculature, proof of mobility or crepitus on palpation could not be obtained. There was least discomfort when the head was in extension. There was moderate muscular spasm of the posterior neck muscles. There was little subjective discomfort at the sight of injury. The skin was intact. Without going into the details of the paralysis, it suffices to state that there was a loss of muscular sensory and reflex power below the level of the distribution of the sixth cervical nerve roots.

There was a sharp line of loss of power and sensation, and reflexes were abolished below this level, roughly complete paralysis below the clavicles and of the arm muscles, except the supinators and deltoid.

There was no zone of hyperesthesia.

Lumbar puncture showed bloody fluid under no tension.

X-ray taken January 31 showed fracture of the posterior arch of the sixth cervical vertebra.

*Treatment*—Surgical advice obtained was unfavorable to operative interference. Treatment consisted of attention to the bladder and general nursing care. On the nights of February 1 and 2 atropin, gr 1/100, was given hypodermically on four occasions to assist the respiration which became suddenly labored and dyspneic.

*Course and Termination*—The patient remained alert and intelligent and in but moderate discomfort. The pain in the back of the neck gradually increased from day to day. On the morning of February 3 there was a sudden increase in dyspnea. There were signs of accumulation of fluid in the lungs and the patient died of failure of respiration at 6 15 a. m.

From the time of admission for forty-eight hours the temperature ranged from 97.8 to 96.2 F. After that the temperature deep within the rectum (3 inches from the anus) was always a little over or under 90 F.

The pulse ranged from 80 to 44, the latter rate being recorded five hours before death, it was always small and compressible. The respiration ranged from 18 to 24, the rate being 26 for a few hours before death.

The blood-pressure was not taken until January 31, and it was then 88 mm Hg. On other occasions it varied but a few millimeters from 90.

*Necropsy*—The necropsy, performed at 11 a. m., February 3, by Dr Otto Schultz, confirmed the diagnosis. There was ecchymosis in the deep muscles of the neck posteriorly. There was a complete separation of the posterior arch of the sixth cervical vertebra with an overriding of the seventh on the sixth, and a fracture without displacement of the right side of the arch of the fifth cervical vertebra where the arch leaves the body of the vertebra. There was gross evidence of injury to and slight softening of the cord at the site of the injury, i. e., between the sixth and seventh vertebræ. There was a little blood in the spinal canal. The brain and cord were removed for subsequent study. There was no evidence of edema in the lungs. Nothing was found to explain the dizziness preceding the accident.

There were no lesions found in any other organs which bear in any way on the report of the case.

I have found no report of a case of fracture of the spine in which low temperature and low blood-pressure were observed, nor have I been able to learn of such observations by personal inquiry and correspondence with surgeons who have had much experience in spinal surgery. Such hypothermia and hypotonia should follow complete severance of the cord just below the phrenic nerve origins. By such breaks in the connection between the medullary vasomotor and heat regulating centers

and so large a part of the body, all vasomotor tone and heat regulation in the body below that part should be abolished. It is a common physiological observation that section of the cord at the sixth cervical vertebra in dogs and rabbits and cats will cause an immediate fall in blood-pressure, which is only in part recovered from in these animals by resumption of vasomotor control by the subsidiary spinal and ganglionic centers below the point of section. What is less known is that Nebelthau in 1895 found, on section of the cord in rabbits between the sixth and seventh cervical vertebrae, that there was a prompt and marked fall in body temperatures and that this is due to a marked diminution of heat production and heat elimination. After section of the cord in this way he was unable to develop fever in spite of injections of erysipelas cultures of the pig. In 1881 Mendelson<sup>1</sup> found the same fall in temperature as a result of the effect of morphin, chloral and curare in dogs and the same failure to develop fever by the injections of pus, hay infusion, and pepsin in such animals. In both cases there is apparently an interference, in Nebelthau's<sup>2</sup> cases, with the path from the centers to the periphery, and in Mendelson's cases, with the activity of the centers and the ability to cause muscular contraction.

The case above reported seems to give clinical support to two important experimental observations in spite of the absence of control records. Unfortunately I cannot offer records of the temperature and blood-pressure in my case before the accident. Two clinical lessons may be drawn from this case. First, that in the injuries to the cord in the vicinity of the sixth and seventh cervical vertebrae the presence of hypothermia and hypotonia would go far to prove that there was a complete separation of the cord from the medulla, or that even if there were sensory and motor paralysis pointing to a complete transverse lesion of the cord at that level, there would be a fair inference that the separation or destruction was not complete if hypothermia and hypotonia were absent. By separation I mean functional and not necessarily anatomical. Second, that it will be well to be on our guard against the existence of complicating lesions in such cases as I have reported because it would seem quite possible that even severe inflammatory processes usually accompanied by fever might occur without the warning of a rise of temperature. It is possible that the slow heart rate in this case was a secondary result of the low temperature, for one should have expected a compensatory increase of heart rate in a patient with such a low blood-pressure and the lesion did not involve the reflex cardiac nervous mechanism at all.

120 East Sixty Second Street

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1 Mendelson *Am Jour Med Sc*, 1883, new series, lxxvi, 380

2 Nebelthau *Ztschr f Biol*, 1895, new series, viii, 293

# THE RELATION BETWEEN ACUTE INFECTIOUS DISEASES AND ARTERIAL LESIONS \*

CHANNING FROTHINGHAM, JR., M D  
BOSTON

The object of this study has been to find whether, during the course of the different acute infectious diseases, any general lesion can be found in the arterial system which seems surely to be the result of the toxins of the disease or of a wide-spread distribution of the infective agent. Furthermore, if such a lesion does exist, is it of a kind that will result on healing in a permanent injury to the arterial system?

That the infective agent may lodge locally in the arterial wall has been shown by the reports of cases in which the tubercle bacilli and the spirochetes of syphilis have been found in human arteries. Wooley<sup>1</sup> has recently reported a case and refers to the other cases reported in which the tubercle bacilli have invaded the intima of the aorta in one or more places from the blood stream. Wright<sup>2</sup> and Richardson were among the first to demonstrate the *Treponema pallidum* in the wall of the aorta in syphilitic aortitis. Also, as Osler points out in his "Modern Medicine," localized acute arteritis may occur in which the invading organism can be demonstrated. Rhea<sup>3</sup> recently reported lesions in arteries of the meninges in a case of hydrocephalus and brain abscess, following an acute influenzal meningitis. This lesion consisted in marked connective tissue thickening of the intima, occluding more than half the vessel's lumen. In this case no organisms were found in the arterial walls, so it is not known whether these lesions were due to the actual presence of the influenza bacillus or to concentrated toxic action followed by thrombus formation and organization. Robertson<sup>4</sup> and Chesley describe a degeneration in the vessel walls in the spinal cord in cases of acute anterior poliomyelitis. Here again it is uncertain whether this action is due to the actual presence of some organism or to some toxin. Thus it is evident that infective agents and possibly their toxins may cause local lesions of a permanent character in arteries. The next question is whether these agents or toxins can cause a diffuse lesion. In

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\*From the Laboratory of the Department of Theory and Practice of Physic, Harvard University. Published with the approval of the committee as work done under a Bullard Fellowship.

1 Wooley. Bull. Johns Hopkins Hosp., 1911, xxi, 82.

2 Wright and Richardson. Boston Med. and Surg. Jour., 1909, clx, 539.

3 Rhea. Reported American Assn. Path. and Bact., 1910.

4 Robertson and Chesley. THE ARCHIVES INT. MED., 1910, vi, 233.

the literature almost all of the infectious diseases are accused of causing degenerative or proliferative changes in the aorta and other vessels. Thus Osler in his "Modern Medicine" in the chapter on arteriosclerosis considers that the acute infections form one of its etiological factors. He says that in scarlet fever, measles, diphtheria, small-pox and influenza foci of arterial degeneration occur with great frequency. In typhoid fever areas of necrosis and fatty degeneration are met in the aorta. Huchard<sup>5</sup> in 1891 and his school considered that the acute infectious diseases of childhood were largely responsible for the arteriosclerosis of adult life. Hofbauer<sup>6</sup> in 1903 reports on the development of arteriosclerosis in a boy of 17 after an attack of measles. Thayer<sup>7</sup> and Thayer<sup>8</sup> and Brush in 1904 present evidence that there is some relation between typhoid fever and alcoholism on the one hand and the development of arteriosclerosis on the other. Wiesner<sup>9</sup> found extensive calcification in the coronary arteries of young people following endocarditis or prolonged osteomyelitis. Wiesel<sup>10</sup> made extensive studies of the heart and blood vessels of young persons in typhoid fever, scarlet fever, measles, diphtheria, sepsis, pneumonia and osteomyelitis. He found in thirty out of 300 autopsies signs of arteriosclerosis in both larger and smaller vessels. The lesions in the media were similar to those found in experimental arterial disease in rabbits. Adam<sup>11</sup> agrees that in burns and acute infections it is common to find fine fatty streaks in the aorta. Fremont-Smith<sup>12</sup> considers that arterial disease is common in the young and that the media is usually primarily involved. Symmitsky<sup>13</sup> in 138 autopsies on people under 25 years of age who died of acute infections found sclerotic changes in the aorta in thirty-eight. If patients under 2 years of age were left out in which he found no lesions, the sclerosis in the aorta occurred in 48 per cent of these cases.

Turning to the experimental side, there is considerable evidence in favor of the possibility of toxins or their causative agents producing arterial lesions. After injury to the aorta, Gilbert<sup>14</sup> and Lion in 1889 succeeded in causing aortic lesions by the injection intravenously of typhoid bacilli and a malignant bacillus isolated from a human case. Since that time several authors have published reports of the successful production of arterial lesions in rabbits by the use of different toxins

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5 Huchard *Rev gén de clin et de therap*, 1891, v, 637

6 Hofbauer *Wien klin Wchnschr*, 1903, xvi, 983

7 Thayer *Am Jour Med Sc*, 1904, cxxvii, 391

8 Thayer and Brush *Jour Am Med Assn*, 1904, xliii, 726

9 Wiesner *Wien klin Wchnschr*, 1906, xix, 725

10 Wiesel *Wien klin Wchnschr*, 1906, xix, 723

11 Adam *Am Jour Med Sc*, 1909, cxxxviii, 485

12 Fremont Smith *Am Jour Med Sc*, 1908, cxxxv, 199

13 Symmitsky *Ztschr f Heilk*, Prague, 1903, xxiv, 177

14 Gilbert and Lion *Compt rend Soc de biol*, 1889, p 583, *Arch de méd exper et d'anat path*, 1904, xvi, 73

or bacteria. Among these the following names appear frequently: Crocq,<sup>15</sup> Pernice,<sup>16</sup> Thérèse,<sup>17</sup> Boinet and Romary,<sup>18</sup> Saltykow,<sup>19</sup> Klotz,<sup>20</sup> and Du Val.<sup>21</sup> Klotz finds that different bacteria act differently. Typhoid bacilli and streptococci caused fatty degeneration of the sub-endothelial tissue and also proliferation, while on the other hand diphtheria bacilli produced only a degenerative lesion. Du Val obtained a proliferation of the endothelium with injections of attenuated glanders bacilli. Others mention round cell infiltration in different layers of the arterial wall.

Most of the experimental work has been done on rabbits. Adler<sup>22</sup> says that arterial disease has been reported in the ox, horse and dog. A few of the experimenters have used guinea-pigs and other animals as well as rabbits, notably Pernice, Boinet and Romary, and Thérèse.

From the above reports on human cases and experiments it seems fair to assume that acute infectious diseases may cause some pretty general lesion throughout the arterial system, either from the diffuse action of toxins or from a wide-spread invasion of the arterial system by the infecting organism. The exact nature of these lesions in human cases and their final result has not been so well worked out. In order to throw some light on this phase of the question this study was undertaken.

Pieces of tissue from the aorta, spleen and kidney were taken at random. The tissue had been preserved in Zenker's fluid and 10 per cent liquor formaldehydi. The Zenker's fixed material was mounted in paraffin, cut and stained with eosin and methylene blue, and Verhoeff's elastic tissue stain. The formalin fixed material was cut by the freezing microtome, and stained with Scharlach R for fat. The Scharlach R stained material was very carefully studied as the presence of fat droplets in cells of the arterial walls is one of the earliest signs of injury. It was thought that tissue taken at random from these three parts of the body would show as well as any tissue a general lesion to the arterial system away from the site of the active process of the acute infection.

At first, tissue from people of all ages was studied, but it was soon found that the majority of people above 25 years showed the same arterial lesions whether they died of acute infections or chronic disorders, and furthermore, that these lesions were very similar to those seen during some acute infections in young people.

15 Crocq Arch de méd expér et d'anat path, 1894, vi, 583

16 Pernice Atti d r Accad d scienze med in Palermo, 1895

17 Thérèse Thèse, Paris, 1893

18 Boinet and Romary Arch de méd expér et d'anat path, 1897, ix, 902

19 Saltykow Ziegler's Beiträge, 1908, xlii, 147

20 Klotz Brit Med Jour, 1906, 2, 1767

21 Du Val Jour Exper Med, 1907, ix, 241

22 Adler Am Jour Med Sc, 1908, cxxxvi, 241

In people above 30 years the following lesions were pretty consistently present. In the arteries of the kidneys there were fat droplets in the muscle fibers of the media and occasionally in the intima. In addition there was frequently an increase in connective tissue of the intima. The spleen showed a hyaline-like change in the walls of its smaller arteries usually involving the intima and occasionally involving the media. Around the hyaline material there was no cellular reaction, and it took the fat stain rather feebly. In the muscle fibers of these and larger arteries there were fat droplets. In the media of the aorta fat droplets were present in the muscle fibers. In the intima there were thickened areas, and in these thickened areas fat. Also there was fat scattered pretty generally along the intima. At the places in the media corresponding to the thickened places in the intima the fat droplets were much more frequent in the muscle fibers suggesting a more marked degeneration of the muscle at these points. In the thickened intima endothelial cells were frequently present and around the vasa vasorum round cell infiltration in slight amount occurred.

No other lesions which could be attributed to acute toxic action were noted. In some cases marked increase in fibrous connective tissue occurred which at times replaced the muscle to considerable extent. In other cases calcareous spots were found. It seemed reasonable to assume, however, that these lesions were the result of some former process, and not due to an acute infection.

Between the ages of 30 and 65, three cases of typhoid, one of pneumonia, one of sepsis, and four of local or general peritonitis were studied as representatives of acute infections, while five cardiac cases, two of nephritis, one of cancer, one of aneurism and one cerebral case as examples of chronic non-infectious disorders. From a study of these cases it soon became evident that the lesions described above were quite generally distributed through both series, and that in order to draw any conclusions in regard to acute infections, selected cases should be studied in which chronic disorders could be practically eliminated.

For this purpose a series of fifty-six subjects under 25 years of age were studied. Most of them died from acute infectious diseases, but there were a few infants and others who died of non-infectious illnesses. There were a few infants and others who died of non-infectious illnesses. In each of these fifty-six cases it was not possible to obtain tissue from all the three parts of the body which had been preserved in both fixatives. Six cases of tuberculosis were studied, one of which was that of an infant 11½ years old. The arteries in this infant were negative throughout; a fact which was noted in practically all the infants, no matter what was the cause of death. In the kidneys of the remaining five subjects there was an increase in the connective tissue of the intima of the arteries in three, and in these cases fat droplets were present in



the muscle fibers of the media. The other two cases showed apparently normal arteries in the kidney. Of these two only one was stained for fat, and that was negative. In the spleens of these five cases a hyaline degeneration of intima and media was present which took a feeble fat stain. In four of the five, fat droplets were present in the media muscle fibers. Only three aortas were preserved. They all showed a thickening of the intima. In two of these formalin tissue was preserved, and they showed fat in the intima and fat droplets throughout the muscle fibers of the media.

Two cases of typhoid fever were studied. The arteries in the kidney appeared normal except for a very rare fat droplet in the muscle fibers. In the spleen one showed a slight hyaline degeneration with no droplets of fat in the media fibers, and the other showed no hyaline degeneration and an exceedingly rare fat droplet in the media. In the aorta of both there was a slight increase in thickness of the intima with fat present and fat droplets in the muscle fibers of the media. These subjects were 21 and 24 years old, and are valuable as controls in that their renal and splenic arteries were so nearly normal.

Of four pneumonia cases, one was in an infant 10 months old which showed normal arteries throughout. Another patient was  $1\frac{2}{3}$  years old. In this case there was no aorta preserved. The renal arteries were negative and also the splenic vessels except for a slight hyaline degeneration. The other two cases showed an increase of connective tissue in the renal arteries with fat droplets in the muscle fibers. In the spleen there was hyaline degeneration which took the fat stain in both cases, and one of them also showed fat droplets in the muscle fibers. Both aortas showed an increase in the thickness of the intima with fat present and fat droplets in the muscle fibers of the intima.

Three of the ten diphtheria patients were under 2 years of age, and showed normal arteries throughout, although the spleen and aorta were only preserved in two. Of the remaining seven cases, six showed normal kidney arteries, and one showed a slight increase in connective tissue and fat droplets in the muscle fibers. This patient was 25 years old, however. In the spleen all seven cases showed hyaline degeneration which took the fat stain, and three of them showed fat droplets in the muscle fibers of the media. The material from the aorta in this series was rather scanty. Four out of five showed thickening of the intima. Five out of six showed fat in the intima and two out of six showed fat droplets in the muscle fibers of the media.

The next group of twelve is composed of septic cases such as peritonitis, osteomyelitis, endocarditis, bronchopneumonia, etc. Of these twelve, one only showed a suggestion of increased connective tissue in the kidney arteries, and two only showed fat droplets in the muscle

fibers of the arteries Seven cases showed the usual hyaline degeneration in the splenic arteries and five did not Only one of these twelve showed fat droplets in the muscle Ten aortas in this group were examined, of which six showed some thickening in the intima with fat drops, while in four the intima was apparently normal Two of the ten showed fat droplets in the muscle fibers of the media

In two cases of measles, the subjects being under 2 years of age, the arteries were normal in all the tissues examined

One case of acute poliomyelitis presented normal arteries Another which was complicated with status lymphaticus showed normal renal arteries, normal splenic arteries except for slight hyaline degeneration, and in the aorta thickening of the intima with fat drops, but no fat droplets in the media

Two cases of meningitis, one of which was a chronic influenzal meningitis, were normal throughout The influenzal case is interesting, as it is the same case that is mentioned above in which Dr Rhea found lesions in the meningeal vessels which strengthens the view that toxins may act locally and not in a general manner

Three cases of bronchopneumonia in infants showed normal arteries

Of two patients with scarlet fever, one aged 3 showed normal arteries throughout The other showed necrosis of the whole arterial wall with fibrin formation and cellular reaction in some of the renal vessels, while the other renal vessels were apparently normal These necrotic vessels showed fat present In the splenic arteries there was slight hyaline change which took the fat stain but no fat droplets in the muscle fibers The aorta appeared normal with the eosin and methylene-blue stain There was no formalin material from which to make a fat stain

One case of glanders in a man 25 years old showed normal amount of connective tissue in the renal arteries but fat droplets in the muscle fibers The splenic arteries showed hyaline degeneration but no droplets in the muscle fibers In the aorta the intima was thickened and had fat in it, and the muscle fibers of the media contained droplets which were much more marked close beneath where the intima was thickened

Five infants under 9 months who died from such obscure causes as inanition, ileocolitis, petechial hemorrhages, etc, failed to show any lesions in the aorta or arteries of the kidney and spleen

Five cases, one chronic nephritis, one hydrocephalus, one congestion and edema of lungs, and two cardiac cases, were used as controls Of these five, the nephritis case alone showed a lesion of the renal vessels This case showed connective tissue increase in the arterial wall and fat droplets in the muscle In the spleen, two of the five showed the usual hyaline degeneration, and one of the four in which there was normal-dehyd tissue showed fat droplets in the media muscle fibers In the

aorta the intima was thickened in four cases, and these cases showed fat in the intima. These four also had fat droplets in the muscle fibers of the media. The other one showed a normal aorta.

From a study of these fifty-six subjects it is evident that the same lesions exist in their arteries as in the older subjects that died of acute or chronic diseases. Therefore, there is no general arterial lesion peculiar to the toxins of the acute infectious diseases. As no evidence of bacteria was found in any of these lesions it seems probable that these lesions, if due at all to the infectious diseases, must be the result of toxic action.

A peculiar feature in the action of toxins is showed in the scarlet fever case in which part of the renal arteries were normal, while others showed extensive necrosis. Apparently in this case the toxin had a selective action for certain of the vessels. A study of this case in detail will be reported in another communication.

The facts that practically no lesions were found in cases under 2 years of age, that the lesions differed in the different tissues, and that the arteries in the three sets of tissue were not equally affected in each case, argue against the supposition that these lesions are caused by toxins of the acute infectious diseases.

On the other hand, the frequency with which these lesions occur in certain groups of cases makes it seem very probable that there is a relation between them and the acute infectious diseases.

In considering only the acute infectious cases (infants and others), the kidney was studied in forty-six cases, in seven of which there was connective tissue increase and in eleven fat droplets in the media. Eight of the eleven cases with fat droplets were in cases of typhoid fever, tuberculosis, pneumonia and glanders. These patients, however, were all nearly 25 years old. It seems reasonable, therefore, to state that as a result of acute infections connective tissue increase in the renal arteries is not to be expected, nor is any fatty degeneration of the media probable except possibly in typhoid fever, glanders, pneumonia and tuberculosis.

In this series the spleens from forty-five cases of acute infection were examined. Of these, twenty-six showed a hyaline degeneration involving either the intima or media or both, which lesion stained poorly with the fat stain. Ten of the forty-five showed fat droplets in the muscle fibers of the media. The hyaline change occurred in 100 per cent of the cases of tuberculosis, pneumonia, diphtheria and glanders with the exclusion of subjects under 1½ years.

In the septicemia group only 58 per cent showed this change. The fat droplets of the media fibers were more unevenly distributed (as regards the disease) than in the renal arteries, and therefore are even less characteristic of acute infections than in the renal arteries. On the other hand, the hyaline change seems quite characteristic of cer-

tain acute infections, and must have some relation to the toxins of the disease, because in some long illnesses in which metabolic disturbances might be expected it does not occur

The aortas were examined in thirty-six cases, twenty-one of which showed thickening of the intima with fat in nineteen of them. The fat was usually more marked in the thickened areas. Eleven of them showed fat droplets in the media muscle fibers. In 100 per cent of the cases of tuberculosis, typhoid, pneumonia and glanders, with the exception of subjects under 11½ years, the intimal lesion was present. It was present also in most of the diphtheria and septic cases. Here again, as there were cases of other acute illnesses in which the lesion did not occur, it seems probable that there is some relation between the acute infection and the lesion.

The next point to consider is what will be the final result of these lesions. Will the lesion on healing leave the arterial system permanently impaired?

The lesion of the fat droplets in the muscle fibers of the media should clear up without permanent injury except in those fibers in which actual necrosis has occurred. If necrosis has occurred there is probably some injury also to the fibroblasts, and connective tissue replacement of the necrotic muscle will occur.

The hyaline degeneration in the intima and media of the splenic arteries probably will not return to normal without leaving some sclerosis. In the intima of the aorta, fat without thickening may return to normal without leaving permanent evidence of a former lesion, but when the intima is thickened, either from edema, infiltration with endothelial cells containing fat, or connective tissue overgrowths, it probably will not resume its former condition, but will always show more or less sclerosis. Therefore, these lesions, which from their frequency probably bear some relation to acute infectious diseases, may leave a permanent change in the arterial system.

If, as some assert, the arteriosclerosis of old age is due to pressure relations, it is perfectly possible for these above described lesions to impair the elasticity of the vessel walls and change the size of the lumen of the vessels and thus effect the pressure relations. The sclerosed patches resulting from these lesions may impair the nourishment to the arterial wall so that a gradually progressing degeneration of the arterial system goes on which may be the cause of arteriosclerosis of old age. The sclerosis of old age may simply be a summation of lesions of this nature arising from infections or metabolic toxins in which case these lesions would play their share in the formation of the arteriosclerosis of old age.

On the other hand, these lesions, after becoming sclerosed, may have no further effect on the arterial system. The arteriosclerosis of old age

may be a disease which has an etiology entirely independent of any of the above-mentioned factors

At the time when this study of human material was being carried on, an attempt was made to produce lesions in animals by the use of toxins. As so much discussion has been raised over the use of rabbits for experimental arterial lesions, guinea-pigs were used in this work. Some experimenters have used this animal and report positive results.

Guinea-pigs under 3 months of age were injected with vaccines of typhoid bacilli and staphylococci. These vaccines were not especially virulent, and could be given in large doses without causing the death of the guinea-pig. Three pigs were injected on five successive days with doses varying from 2,500 to 5,000 million dead staphylococci, and three others on the same days with from 2,500 to 7,000 million dead typhoid bacilli. On the sixth day these animals were killed instantaneously without anesthesia, together with three control animals. Tissue from the aorta, kidney and spleen was preserved, cut and stained just as the human material. No lesions were found in the vessels of either set of animals nor in the controls, except in the aorta of one guinea-pig injected with staphylococci, in which a thickening of the intima with connective tissue at one place occurred. Three guinea-pigs were also injected with the same amount of staphylococcus vaccine, and three others with the same amount of typhoid vaccine twice a week over a period of two months in order to see if a more prolonged action would have any effect. Both these sets of pigs were smaller and thinner than the controls kept under the same conditions, which suggested that these animals were influenced by the action of the toxins. These pigs and the controls were killed, and their tissues preserved and studied in the same manner as the others, but no lesions were discovered in the arteries.

Some experiments were done with white rats by injecting living cultures of diphtheria and typhoid bacilli and staphylococci, and also by injections of 95 per cent alcohol. A few of the rats were quite old and the others young. As no arterial lesions appeared in any of the animals, the details of the experiments will not be recorded here.

It seems fair to conclude that in certain of the acute infectious diseases, diffuse arterial lesions exist which may be the result of toxic action. In other acute infections no arterial lesions occur. Some of these lesions will undoubtedly leave on healing a permanent sclerosis in the arterial system.

Toxins will cause arterial lesions locally at the site of the active process of the infectious disease (other authors) or locally in some distant organ such as the kidney, as was seen in the above case of scarlet fever.

Of the acute infections, diphtheria, pneumonia, tuberculosis, typhoid and glanders seemed most consistently to have associated with them general lesions in the arteries of at least one of the tissues examined

Attempts to produce widely distributed arterial lesions in guinea-pigs and rats by means of certain bacterial toxins failed

For the material and many kind suggestions I am indebted to Dr  
F B Mallory

51 Hereford Street

# THE DIAGNOSTIC IMPORTANCE OF ALBUMIN AND ALBUMOSE IN THE SPUTUM AND THEIR RELATION TO OCCULT BLOOD \*

EDWARD H. GOODMAN, M.D.  
PHILADELPHIA

Researches in the chemistry of the sputum have not kept pace with those made in the study of the excretions and secretions of other organs of the body, and what has been done has not been found of much value to clinicians, partly because of elaborate technic and partly because of uncertainty in results obtained.

For a critical review of the work published along this line the reader is referred to an article by Wanner,<sup>1</sup> in which he reports a comprehensive study of the sputum from various pulmonary conditions, such as chronic bronchitis, bronchiectasis, pulmonary tuberculosis, pulmonary infarct, gangrene and pneumonia, devoting special attention to the albumin and albumose content.

He regards any albumin reaction which is more than a slight opalescence as pathological, and if there is any albumin with the heat and acid test, then the sputum ceases to be a secretion. In other words, the underlying morbid process is not bronchitis. In distinguishing between this condition and pulmonary tuberculosis, the presence of albumin speaks unconditionally in favor of tuberculosis.

As to the origin of albumin, Wanner calls attention to three sources from which it may be derived, namely, from the glands of the mucous membrane, from the blood-vessels of the bronchial tree, and from ulceration of the bronchi or the lung parenchyma. Albumose he regards as a split product of albumin, produced by bacteria and autolysis.

Recently Roger and Levy-Valensi<sup>2</sup> have called attention to the value of examining sputa for albumin and they claim to have discovered in the qualitative detection of protein a uniformly reliable means of diagnosing tuberculosis from bronchitis, pulmonary emphysema and conditions as syphilis, gangrene and cancer. Their studies have been

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\*From the laboratory of Dr. John H. Musser.

\*Read before the Pathological Society of Philadelphia March 23, 1911.

1 Wanner. *Beiträge zur Chemie des Sputums*, *Deutsch. Arch. f. klin. Med.*, 1903, LXXV, 347.

2 Roger and Levy-Valensi. *Albumino réaction des expectorations*, *Presse med.* 1910, p. 289.

corroborated by Wourmann, Oddo and Gachet, and by Coinu (all quoted by Roger)<sup>2</sup> and most recently by Geeraerd<sup>3</sup>

The last-named author is particularly enthusiastic about the test and goes so far as to say that if a case of tuberculosis presents no albumin in the sputum, it is proof of cicatricial contraction, and should albumin appear a new cure should be begun. He lays especial emphasis on coupling the chemical examination of the sputum with the cutaneous reaction, and should albumin and the latter be present, then tuberculosis is present beyond peradventure of a doubt.

The papers of Roger and Levy, and others, were so optimistic about the reliability of the albumin test, and the field of sputum chemistry has been so woefully neglected, that I have been induced to take up studies along similar lines.

Sputa containing macroscopic blood were, of course, discarded, and for our first thirty-five cases this was the only precaution observed. To our surprise practically every sputum contained either albumin or albumose, or both, and my attention was directed to the possible contamination of the sputum by small quantities of blood, which might be invisible macroscopically or microscopically, but which we might recognize by means of a subtle chemical test.

#### TECHNIC

A portion of sputum was collected in a large dry bottle, mixed with equal parts of water, and thoroughly stirred with a glass rod. The sputum should not be allowed to stand in a warm place, since putrefactive changes readily occur and albumin is split off from the mucus.<sup>2</sup> A few drops of acetic acid are now added to precipitate the mucus, and this part of the procedure must be performed with extreme care. To make sure of this, a small portion should be filtered and to the filtrate one or two drops of acetic acid added. If no cloud appears, the precipitation has been complete. Too much acetic acid may prevent the coagulation of albumin.

The sputum is now filtered and, to one portion, saturated salt solution is added, the solution boiled and one or two drops of acetic acid added. In the presence of albumin a cloud appears. To a second portion is added one drop of a saturated solution of potassium ferrocyanid which will precipitate the albumin.

*Albumose*—A portion of the filtered sputum is mixed with an equal portion of a saturated solution of sodium chlorid, boiled and filtered.

<sup>3</sup> Geeraerd. *L'albumino réaction de l'expectoration chez les tuberculeux*, Jour med Bruxelles, 1910, 505



One portion is kept hot and the other cooled, and if albumose is present, there appears a cloud in the cooled portion

*Occult Blood*—Application of the benzidin test was made (Goodman<sup>4</sup>) A portion of the sputum after mixing with equal parts of water is thoroughly shaken with glacial acetic acid The solution is then boiled, cooled and tested with benzidin Occult blood was adjudged present when there was a distinct blue color imparted to the particles of sputum or to the liquid as a whole

The tuberculous cases have been arbitrarily divided into incipient and advanced Under the first heading are grouped those cases of infiltration with but few physical signs, while under the second heading are arranged those cases presenting consolidation of one or more lobes, with or without cavity formation

The first thirty-five cases, in view of the later findings, have been rejected, and in the cases on which our study is based, the following examinations have been made Albumin, albumose, microscopic for erythrocytes, occult blood and tubercle bacilli The cases we have arranged in five tables, a study of which will prove of more than passing interest

In the first place it will be seen that in the vast proportion of cases, occult bleeding, albumin and albumose go *pari passu*, and it must be recognized that minute extravasations of blood constitute the chief source of the albumin content of the sputum

In the second place, microscopic examination of the expectoration in itself does not constitute sufficient data on which to decide whether the sputum does or does not contain blood A final opinion can be reached only after chemical tests have been made

Thirdly, neither albumin nor albumose is in itself significant of pulmonary tuberculosis, since we have found both present in other conditions (bronchitis, asthma, emphysema, pleurisy, heart disease) Its absence is likewise not indicative of the non-tuberculous nature of the condition, since in many cases of tuberculosis, no albumin has been found

An interesting point is that occult bleeding is seen in many cases of incipient tuberculosis and is not a feature alone of the advanced stages It seems to bear no relation to the presence or absence of tubercle bacilli

In fifteen of our cases, either albumin or albumose, or both, were present when no occult blood could be detected, and we have no explanation for this phenomenon Likewise we are at a loss to interpret the four

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<sup>4</sup> Goodman The Examination of the Feces for Occult Blood, with Special Reference to the Value of the Benzidin Test, *Am Jour Med Sc*, 1907



TABLE 2.—ALBUMINURIA AND ALBUMINEMIA

No.	Albumin	Albumose	R B C	Occult	Blood	T	B	Diagnosis
1	+	0	0	0	0	0	0	Pneumonia
2	+	0	0	0	0	0	0	Pneumonia
3	+	0	0	0	0	0	0	Pneumonia
4	+	0	0	0	0	0	0	Pneumonia
5	+	0	0	0	0	0	0	Pneumonia
6	+	0	0	0	0	0	0	Pneumonia
7	+	0	0	0	0	0	0	Pneumonia
8	+	0	0	0	0	0	0	Pneumonia
9	+	0	0	0	0	0	0	Pneumonia
10	+	0	0	0	0	0	0	Pneumonia
11	+	0	0	0	0	0	0	Pneumonia
12	+	0	0	0	0	0	0	Pneumonia
13	+	0	0	0	0	0	0	Pneumonia
14	+	0	0	0	0	0	0	Pneumonia
15	+	0	0	0	0	0	0	Pneumonia
16	+	0	0	0	0	0	0	Pneumonia
17	+	0	0	0	0	0	0	Pneumonia
18	+	0	0	0	0	0	0	Pneumonia
19	+	0	0	0	0	0	0	Pneumonia
20	+	0	0	0	0	0	0	Pneumonia
21	+	0	0	0	0	0	0	Pneumonia

TABLE 3.—ALBUMINURIA AND ALBUMINEMIA

No.	Albumin	Albumose	R B C	Occult	Blood	T	B	Diagnosis
1	+	0	0	0	0	0	0	Pneumonia
2	+	0	0	0	0	0	0	Pneumonia
3	+	0	0	0	0	0	0	Pneumonia
4	+	0	0	0	0	0	0	Pneumonia
5	+	0	0	0	0	0	0	Pneumonia
6	+	0	0	0	0	0	0	Pneumonia
7	+	0	0	0	0	0	0	Pneumonia
8	+	0	0	0	0	0	0	Pneumonia
9	+	0	0	0	0	0	0	Pneumonia
10	+	0	0	0	0	0	0	Pneumonia
11	+	0	0	0	0	0	0	Pneumonia
12	+	0	0	0	0	0	0	Pneumonia
13	+	0	0	0	0	0	0	Pneumonia
14	+	0	0	0	0	0	0	Pneumonia
15	+	0	0	0	0	0	0	Pneumonia
16	+	0	0	0	0	0	0	Pneumonia
17	+	0	0	0	0	0	0	Pneumonia
18	+	0	0	0	0	0	0	Pneumonia
19	+	0	0	0	0	0	0	Pneumonia
20	+	0	0	0	0	0	0	Pneumonia
21	+	0	0	0	0	0	0	Pneumonia

TABLE 4.—ALBUMINURIA AND ALBUMINEMIA

No.	Albumin	Albumose	R B C	Occult	Blood	T	B	Diagnosis
1	+	0	0	0	0	0	0	Pneumonia
2	+	0	0	0	0	0	0	Pneumonia
3	+	0	0	0	0	0	0	Pneumonia
4	+	0	0	0	0	0	0	Pneumonia
5	+	0	0	0	0	0	0	Pneumonia
6	+	0	0	0	0	0	0	Pneumonia
7	+	0	0	0	0	0	0	Pneumonia
8	+	0	0	0	0	0	0	Pneumonia
9	+	0	0	0	0	0	0	Pneumonia
10	+	0	0	0	0	0	0	Pneumonia
11	+	0	0	0	0	0	0	Pneumonia
12	+	0	0	0	0	0	0	Pneumonia
13	+	0	0	0	0	0	0	Pneumonia
14	+	0	0	0	0	0	0	Pneumonia
15	+	0	0	0	0	0	0	Pneumonia
16	+	0	0	0	0	0	0	Pneumonia
17	+	0	0	0	0	0	0	Pneumonia
18	+	0	0	0	0	0	0	Pneumonia
19	+	0	0	0	0	0	0	Pneumonia
20	+	0	0	0	0	0	0	Pneumonia
21	+	0	0	0	0	0	0	Pneumonia

TABLE 5.—ALBUMINURIA AND ALBUMINEMIA

No.	Albumin	Albumose	R B C	Occult	Blood	T	B	Diagnosis
1	+	0	0	0	0	0	0	Pneumonia
2	+	0	0	0	0	0	0	Pneumonia
3	+	0	0	0	0	0	0	Pneumonia
4	+	0	0	0	0	0	0	Pneumonia
5	+	0	0	0	0	0	0	Pneumonia
6	+	0	0	0	0	0	0	Pneumonia
7	+	0	0	0	0	0	0	Pneumonia
8	+	0	0	0	0	0	0	Pneumonia
9	+	0	0	0	0	0	0	Pneumonia
10	+	0	0	0	0	0	0	Pneumonia
11	+	0	0	0	0	0	0	Pneumonia
12	+	0	0	0	0	0	0	Pneumonia
13	+	0	0	0	0	0	0	Pneumonia
14	+	0	0	0	0	0	0	Pneumonia
15	+	0	0	0	0	0	0	Pneumonia
16	+	0	0	0	0	0	0	Pneumonia
17	+	0	0	0	0	0	0	Pneumonia
18	+	0	0	0	0	0	0	Pneumonia
19	+	0	0	0	0	0	0	Pneumonia
20	+	0	0	0	0	0	0	Pneumonia
21	+	0	0	0	0	0	0	Pneumonia

TABLE 3—NON-TUBERCULOUS CASES (Continued)

No	Albumin	Albumose	R B C	Occult Blood	T B	Diagnosis
22	0	0	0	0	0	Bronchial asthma
23	0	0	0	0	0	Pleurisy
24	+	+	0	Very slight trace	0	Pleurisy
25	+	+	0	Slight trace	0	Empyema
26	+	+	0	Very slight trace	0	Gastritis
27	+	0	Few	Trace	0	Hyperchlorhydria
28	+	+	Few	Trace	0	Heart disease
29	0	+	0	0	0	Hereditary syphilis

TABLE 4—TUBERCULOUS CASES WITH ALBUMIN AND ALBUMOSE BUT NO OCCULT BLOOD

No	Albumin	Albumose	R B C	Occult Blood	T B	Diagnosis
1	+	+	0	0	+	Advanced
2	+	+	0	0	+	Advanced
3	+	+	0	0	0	Incipient (healed)
4	+	+	0	0	0	Incipient (healed)
5	Slight tr	Slight tr	0	0	0	Incipient (healed)
6	+	+	0	0	+	Incipient (healed)
7	+	+	0	0	+	Incipient (healed)
8	+	0	0	0	0	Incipient (healed)
9	0	Trace	0	0	0	Incipient (healed)
10	+	+	0	0	0	Incipient (healed)
11	+	+	0	0	?	Incipient (healed)
12	+	+	0	0	0	Incipient (healed)

TABLE 5—NON-TUBERCULOUS CASES WITH ALBUMIN AND ALBUMOSE BUT NO OCCULT BLOOD

No	Albumin	Albumose	R B C	Occult Blood	Diagnosis
1	+	+	0	0	Pneumonia
2	+	+	0	0	Pneumonia
3	0	+	0	0	Hereditary syphilis

TABLE 6—CASES OF OCCULT BLOOD BUT WITH NO ALBUMIN OR ALBUMOSE

No	Albu- min	Albu- mose	R B C	Occult Blood	T B	Diagnosis
1	0	0	0	Slight tr	0	Advanced tuberculosis
2	0	0	0	Slight tr	0	Bronchitis
3	0	0	0	Very slight tr	0	Incipient tuberculosis
4	0	0	0	Trace	0	Pneumonia

I am indebted to Drs Landis, Francine, Corson and T Mellor Tyson for placing material at my disposal. Use has been freely made of sputa obtained from cases in the private practice of Dr Musser and in his ward in the Presbyterian Hospital.

248 South Twenty-first Street

# EXPERIMENTS WITH THE INTRAVENOUS INJECTION OF SALVARSAN IN ACID SOLUTION \*

J AUER, M D  
NEW YORK

## INTRODUCTION

In the vast literature already existing about Ehrlich's wonderful discovery there is little experimental evidence on the action of salvarsan in acid solution when given intravenously. The drug has been occasionally given in this form to human beings by a few clinicians, but their results need not concern us here, for it is obvious that the best method for administering an admittedly toxic substance cannot be thoroughly tested on human beings. These considerations made it desirable to investigate this aspect of the subject, and therefore the tolerance of rabbits for salvarsan was tried out when this substance was dissolved in 0.9 per cent salt solution and injected intravenously. Practically the only experimental contribution which demands consideration here has been the work of Hering,<sup>1</sup> who tested the effect of 606 when dissolved in 0.9 per cent saline so as to form a 0.5 per cent solution.

This solution was infused through the jugular vein of rabbits and dogs, and their blood-pressure recorded. This author found that 4 to 5 mg per kilo rabbit, infused during five to ten minutes, caused death one-half to two minutes after stoppage of the infusion. Similar results were obtained with dogs. On the basis of this experimental evidence he warns earnestly against the employment of acid solutions in human therapeutics. In the following pages experimental evidence will be brought forward to show that Hering's warning is applicable only to the acid solution in 0.5 per cent strength, it emphatically does not apply to the acid solution of salvarsan when sufficiently dilute, for example, in a strength of 0.1 per cent.

## EXPERIMENTS

*Methods*—All the experiments were carried out by the intravenous infusion of the drug in rabbits. The solutions were injected either into the jugular vein or the marginal ear vein. When the injection was given into the jugular vein, the animal was first etherized, in order to insert the venous and arterial cannulas. After recovery from the anesthetic, the solution was allowed to flow into the vein from a Mariotte burette at

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\*From the Department of Physiology and Pharmacology of the Rockefeller Institute

1 Hering. *Munchen med Wehnschr*, 1910, lvi, 2621

a pressure of about 15 cm of water. The blood-pressure was usually recorded by a mercury manometer connected with the carotid artery, the tubing being filled with a half-saturated solution of sodium sulphate.

The solution of salvarsan was always prepared by grinding the powder in a sterile mortar with gradually increasing quantities of sterile 0.9 per cent saline, until a clear solution of the required strength was obtained. This initially clear solution always showed a moderate opalescence after some hours. After a sealed tube of salvarsan had been opened, the substance was used as a rule within a few hours, if any remained, it was discarded. No solution was ever utilized which had been prepared the

previous day. The first two series of experiments need but little discussion, the main results will be seen in the subjoined tables. In the first series a 0.25 per cent solution of salvarsan was infused through the jugular vein. Both animals died after receiving per kilo respectively 141 and 571 mg. One died twenty-five minutes after stoppage of the infusion, with tonic and clonic convulsions, the other died during the night. In the second series a solution of 0.5 per cent strength was infused slowly through the jugular artery. Four out of five animals succumbed after receiving a much smaller dose per kilo body-weight than when the solution was administered through the vein. Further details will be seen in Table 2.

These two series of experiments show clearly the effect of concentration of solution, on the size of the lethal dose. With a 0.25 per cent strength (Series 1) the animals needed from 40 to 50 mg. per kilo body weight, with a solution twice as strong (viz. 0.5 per cent) the lethal dose varied between 40 and 160 mg. per kilo weight. In other words, if the infused solution was diluted twofold (0.5 per cent to 0.25 per cent) the maximal tolerance was increased fourfold (40 mg. to 160 mg.). It therefore seemed possible that a still greater dilution would permit the infusion of fairly large amounts of salvarsan and yet save the animal. It may be stated at once that this expectation was realized when the infusions were carried out with 0.1 per cent strength. (Table 3) (Series 3) gives a summary of this experiment.

These animals, during and after the infusion of about 12 mg per kilo, were never in any obvious danger. During the infusion the respiration was slowed, but the blood-pressure remained practically at the normal level. All of the animals were in good condition at least sixteen days after the injection. It will be seen, however, that the infusion rate was exceedingly slow, at times less than 0.5 c.c. per minute. The exceeding slowness of this rate will be realized when one considers that 0.5 gm. of salvarsan would thus require over sixteen hours for its infusion. Such a method of introducing a drug is therefore only of academic value, provided that the infusion rate cannot be increased. To test this another

series of experiments was carried out (Series 4) in which the attempt was made to inject large quantities per kilo in a shorter time than in the experiments of Series 3. In addition it was also determined whether the acid solution causes pain and irritation when injected into a superficial vein, especially if some of the solution should escape into the adjacent tissue. These injections were made with 0.1 per cent solutions injected by means of a syringe into the marginal ear vein of non-anesthetized rabbits.

This last series shows very well that a comparatively large dose of salvarsan in acid solution may be injected intravenously with fair rapidity in rabbits without causing pain or obviously endangering the animals' lives. The muscular weakness which was noted in Series 3, in which the animals were anesthetized in order to insert cannulas into the external jugular vein and into the carotid artery, was markedly less pronounced in the animals comprising Series 4, when the injections were carried out minus anesthesia or operative interference.

#### DISCUSSION

In the foregoing pages experimental evidence has been submitted which shows that the toxicity of salvarsan in acid solution (viz., simply dissolved in 0.9 per cent saline) when injected intravenously in rabbits varies inversely with the concentration of this substance in the solutions employed. Thus for example, when salvarsan was injected in 0.5 per cent solution (Series 2), four out of five animals died on the holder after receiving 4 to 16 mg. per kilo, while in Series 3, and especially in Series 4, the rabbits tolerated 10 to 22 mg. per kilo in 0.1 per cent solution without any marked evil effects. Moreover, all the animals of these two series (eight rabbits) were alive and well at least sixteen days after the injection. In order to emphasize the amount injected it may be permissible to express this result in terms of a 70-kilo person. Such a person would easily tolerate, on the basis of these data, 0.4 to 1.5 gm. of salvarsan when given intravenously in 0.1 per cent acid solution. It must be emphasized that the above doses for rabbits are by no means the maximal doses of the 0.1 per cent solution which are just tolerated with safety, although I have no experiments to support this statement, it seems probable to me that still larger amounts may be injected before seriously endangering the animal's life.

From the tables of Series 4 it will be seen that the rate of injection is still fairly slow, the fastest rate employed being 6 c.c. per minute, and the slowest about 3 c.c. per minute. This rate can be doubled without trouble or danger. In five reinjection experiments, 20 mg. of salvarsan per kilo in 0.1 per cent solution were introduced through the ear-vein at a rate of 15 c.c. per minute, the animals showed no distress. At this rate 0.5 gm. could be incorporated in a little over half an hour.

TABLE 1—SERIES 1 RABBITS INJECTED WITH 0.25 PER CENT SALVARSAN IN 0.9 PER CENT SALINE, JUGULAR VEIN

No	Color	Sex	Weight	Blood-Pressure Rate Before After of In- Infusion Infu- fusion	Mg per Kilo	Result*
			gm	mm mm mm		
S4	White	F	1,670	114 60 1	41.8	Very weak, next a m found dead
S5	White	F	1,400	100 40 1	57	Strong convulsions after infusion after infusion

Death twenty-five minutes

\*Rate of infusion less than 1 c c per minute

TABLE 2—SERIES 2 RABBITS INJECTED WITH 0.5 PER CENT SALVARSAN IN 0.9 PER CENT SALINE, JUGULAR VEIN

No	Color	Sex	Weight	Blood-Pressure Rate Before After of In- Infusion Infu- fusion	Mg per Kilo	Result*
			gm	mm mm mm		
S3	Gray	F	3,290	90 8 1	8	B-P dropped suddenly after 6.25 c c short convulsions Resp and heart stopped
S6	White	F	1,260	84 66 0.5	16.6	B-P still 66 mm Hg Nov 4 c c of solution ran in swiftly by accident
S7	White	F	1,570	104 72 0.33	12.7	After a three-min stoppage of infusion a few drops of solution caused a sudden fall of B-P to almost zero Death
S8	White	F	1,440	104 66 0.2	6.9	Infusion stopped for 18 min B-P maintained at about 70 mm, now after a few drops of sol B-P dropped to 26 mm Stop in- fusion Recovery
S9	Gray	F	2,470	110 30 0.2	4	B-P slowly sank to 30 mm Convulsions, heart irregular, resp stopped Death

\*B-P means blood pressure



TABLE 3—SERIES 3 RABBITS INJECTED WITH 0.1 PER CENT SALVARSAN IN 0.9 PER CENT SALINE, JUGULAR VEIN

No	Color	Sex	Weight gm	Blood-Pressure Before After Infusion Infu- sion ce per mm mm mm	Rate of In- fu- sion ce per mm	Mg per Kilo	Result
S10	Gray	F	2,790	104	104	0.6	10.7 Moderately weak after infusion, moves about 2 days later Good condition
S11	Gray	F	1,440	100	105	0.5	11.1 Hops about after infusion, some weakness , days later Good condition
S12	Gray	F	1,760	96	90	0.5	14.2 Moderate weakness after infusion Good condition next day
S13	Gray	M	2,330	116	108	0.8	12.8 Moderate weakness after infusion Next day in good condition

TABLE 4—SERIES 4 RABBIT INJECTED WITH 0.1 PER CENT SALVARSAN SOL IN 0.9 PER CENT SALINE, MARGINAL EAR-VEIN

No	Color	Sex	Weight gm	Rate of Infusion ce per mm	Duration of In- fu- sion mm	Mg per Kilo	Result
S14	White	F	2,110	6	5.5	15.5	No struggle or pain during infusion injection Respiration slowed Hops about at once after
S15	Gray	F	1,400	3.6	8	21.4	Perfectly quiet during injection Respiration slowed After the injection
S16	Gray	F	1,350	3.3	9	22.2	quiet, ears erect Two short struggles during injection Resp slowed Moves about
S17	White	F	2,200	3	12	15.9	Slight short struggle during injection after injection, ears erect Moves about after in- jection, ears erect Practically no slowing of respiration

Another point of interest noted in the series of animals which received the drug through the ear-vein was this: none of the animals showed any pain whatsoever during or after the injection, nor did any marked inflammation or necrosis result. This was especially striking in one animal, S17, in which some of the injected solution accidentally infiltrated a small area of tissue. No edema or marked inflammation occurred at any time during the next twelve days. The marginal ear-vein merely became thrombosed, and later showed a slight degree of inflammation, such as is usually observed after any injection into this vein. A much severer reaction at the site of injection was expected because of the technic I employed; the hypodermic needle was always inserted 1.5 to 2 cm into the vein and then anchored by two bulldog clamps which gripped the ear and the needle. This more or less marked crushing of the tissues, especially of the injected vein itself, would surely aid in bringing out whatever irritating qualities the injected solution possessed. In spite of this none of the rabbits showed pain at any time, and in no rabbit did any marked inflammation occur, even when some of the 0.1 per cent solution infiltrated the wall of the vein and the surrounding tissue. In but one rabbit (S16) did moderate edema of the ear occur. This edema was noted within twenty-four hours after the injection and was by no means extreme; twenty-four hours later it had disappeared entirely.

It may be remarked in passing that the acid content of salvarsan is very small, only 83 mg of hydrochloric acid per 0.5 gm. This amount in a 0.1 per cent solution of the drug makes an exceedingly dilute solution of the acid, so dilute that the alkaline tissue juices can have no trouble in reducing and neutralizing the acidity of the solution which escapes into the surrounding tissue. This is an advantage not possessed by the strongly alkaline solutions generally employed.

#### OTHER OBSERVATIONS

While the main object of this investigation was to determine the conditions under which fairly large quantities of an acid solution of salvarsan could be safely infused in rabbits, a number of other data were gathered during the course of the work which are worthy of being recorded.

**Autopsy Notes.**—In practically all the fatal cases in Series 1 and 2 there was an excess of clear yellow fluid in the peritoneal cavity and in the thorax. This was especially well marked in the two rabbits of Series 1. No excess of fluid was seen in the intestine itself. The intestines were, as a rule, pale, while the mesenteric vessels were moderately distended with blood. The lungs in almost all instances showed signs of pulmonary edema, which, however, was never so extreme that foam was found in the trachea. The heart usually was distended with blood when the autopsy was made immediately and was in a state of block, the auricles beating three or four times to one weak ventricular contraction. The blood coagulated readily within three to five minutes.

**Urine.**—Most of the surviving animals voided urine within the twenty-four hours following the injection. In one rabbit only (S8) about forty-eight hours elapsed before urine was passed; this rabbit was the only one which survived when the drug was given in 0.5 per cent solution, all the other survivors belonged

to the 0.1 per cent series. None of the rabbits voided by these surviving rabbits reduced copper solution. Only one rabbit showed sugar in the urine, this was Rabbit 184, which received a very large dose of salvarsan per kilo body-weight. This rabbit died during the night and the urine obtained from its bladder showed 2.5 per cent sugar according to Pavy's method. It will be remembered that this rabbit also showed a large excess of fluid in the peritoneal and pleural cavities.

**End Results.**—All of the surviving rabbits were carefully weighed at regular intervals after the injection. It soon became apparent that the members of the two series, 3 and 4, reacted differently, although both received the drug in the same concentration. The rabbits of Series 3 also showed, during the first few days, a gradual loss of weight which varied between 180 and 230 gm, and normal weight was not regained until about ten days had passed. The rabbits of Series 4, on the other hand, showed in three cases (S14, S15, S16) a gain of weight in three days varying between 180 and 470 gm; this initial increase was well maintained so that two weeks after the injection their weights were still 150 to 300 gm above normal. The fourth rabbit of this series showed a loss of 90 gm one day after injection, but this loss was repaired within five days. It must be added that no surviving rabbit of any series showed diarrhea at any time. This difference in reaction to the same solution, for both series received the drug in 0.1 per cent strength, is probably due to the different methods employed. In Series 3 the animals were subjected not only to the depressing effect of salvarsan but also to the unfavorable action of the ether, operation, etc.; while animals of Series 4 were exposed to the effects of salvarsan alone. This result is interesting in that it indicates that even normal animals when injected with the same solution under different conditions may show fairly striking differences in the end result.

**Fall of Blood Pressure.**—Another point of interest, which was brought out by the blood pressure experiments of Series 2, is this: with fairly concentrated solutions, 20 to 25 per cent, in this instance, the blood pressure may sink profoundly without any warning. In the experiments S3, S7, S8, the blood pressure suddenly dropped markedly. In two animals, this ended with death, one recovered. The blood pressure before this drop was still good, ranging between 65 and 80 mm of mercury, and there was nothing to indicate a weakening of the heart. More over, the fall occurred in two cases on resuming the infusion which had been stopped for a number of minutes. This drop of blood pressure is probably due to a sudden weakening of the heart. These three experiments show well how swiftly a dangerous and even fatal fall of blood pressure may occur with 0.5 per cent solutions, even when infused with extreme slowness.

**Reinjection Experiments.**—A number of the surviving rabbits were again injected with the 0.1 per cent acid solution. Thus S8, S11, S14, S15, S16 received 20 mg of salvarsan per kilo body-weight, sixteen to twenty days after the first injection. The reinjection was given through the marginal ear-vein at a rate varying from 10 to 17 cc per minute. The animals were quiet after the injection, and the respiration was considerably slowed, ranging between 50 and 80 per minute. The temperature always showed a rise of at least 1° C within two or three hours after the injection, the highest temperature obtained was 41.5 C. The average normal temperature was about 39.5 C. This period of fever did not last long as a rule, after less than twenty-four hours the temperature had dropped to normal. It deserves notice that the slow respiratory rate mentioned above was also obtained during the stage of fever. All the rabbits stood the heavy dose of salvarsan very well, and no ill effects were seen except that S16 developed a massive edema of the injected ear, this edema disappeared within three days. In none of the other rabbits did an edema appear. It will be remembered that the same rabbit, S16, reacted with a moderate edema to the first injection of salvarsan.

## RESULTS

Acid solutions of salvarsan, *i e*, salvarsan dissolved in 0.9 per cent saline solution, may be injected intravenously in rabbits with safety provided that the solution is dilute

With a 0.1 per cent solution in 0.9 per cent saline as much as 22 mg and probably more per kilo may be safely infused, this would correspond in a 70 kilo individual to 1.5 gm

Concentrated solutions of salvarsan in saline, *i e*, 0.5 per cent, are dangerous and usually fatal in rabbits even when infused with great care, the fatal dose varies between 4 and 12 mg per kilo. This agrees practically with the experimental results obtained by Hering

The acid solution in 0.1 per cent strength causes no pain or marked inflammation when injected into the ear-vein of rabbits, even when some of the solution infiltrates the surrounding tissue

Hering's energetic warning against the intravenous injection of acid solution of salvarsan in human beings has experimental justification only for 0.5 per cent solutions of the drug. It does not apply to sufficiently dilute solutions, for example, solutions of 0.1 per cent

Attention may be called to the fact that 0.5 gm of salvarsan contains only 0.083 gm of hydrochloric acid, a quantity which corresponds to about 0.25 cc of the ordinary 32 per cent concentrated acid. A 0.1 per cent solution of the drug is therefore only weakly acid. It also must be noted that the tissues of the body are better able to protect themselves against harmful acidity than against harmful alkalinity, against an acid solution the body tissues may mobilize neutralization and dilution, against harmful alkalinity practically only dilution is available, the carbon-dioxid content of most tissues being probably too small to play much of a rôle

Rockefeller Institute

# URINE FORMATION DURING ETHER ANESTHESIA<sup>\*</sup>

P B HAWK, PH D

URBANA, ILL

In a previous paper<sup>1</sup> I reported the data from a series of experiments on the diuresis following ether anesthesia. In those experiments, which were made on dogs, it was shown that ether narcosis induced for periods varying in length from thirty minutes to four and one-half hours was followed in every instance by an initial diuresis, the extent of the diuresis being proportional, in some instances, to the length of the anesthesia period. This point was well illustrated by the initial diureses of 5.7 per cent, 6.8 per cent, 12.9 per cent and 24.8 per cent which followed ether anesthesia periods of one-half, one, two and four and one-half hours respectively. It was further shown in these experiments that the diuretic effect of the ether was persistent in every case except one. The ultimate average daily percentage increase in the urine volume ranged from 3.1 per cent to 20.7 per cent for subsequent intervals of from five to fourteen days.

The data from the experiments mentioned above gave us no information as to the actual conditions of urine formation during the time the animal was under the influence of the anesthetic. It was therefore subsequently determined to investigate the rate of urine formation under ether anesthesia, using in these tests the identical animals utilized in the experiments already mentioned. Three of these animals (Dogs 1, 3 and 5) were therefore made the subjects of the demonstration.

The plan of the experiments here reported was simple. The animal was placed under ether anesthesia, after which the abdomen was opened and cannulas inserted in the ureters. The rate of urine formation was then carefully observed, the volume formed during each hour being accurately measured.

## DISCUSSION OF DATA

The data from the first experiment (Experiment 12) are given in Table 1. The subject of this experiment was Dog 1, a bitch weighing about 5.5 kg. Anesthesia was induced for a period of ten hours and twenty minutes during which time a urine flow aggregating 19.7 c c was registered. During the first two hours a volume of 1.9 c c was collected,

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<sup>\*</sup>From the Laboratories of Physiological Chemistry of the University of Illinois and of the Department of Medicine of the University of Pennsylvania.

<sup>1</sup> Hawk Jour Med Research, 1908, new series, xiii, 203

indicating a total urine formation of 36 c.c. for this period, inasmuch as the two cannulas had a capacity of 17 c.c. The most rapid formation of urine was noted between the fourth and fifth hours of anesthesia. During this interval 5.7 c.c. of urine was formed. Following this hour there was a pronounced decrease in the rapidity of urine formation, as is shown by the subsequent collection of fractions of 4.1 c.c. and 2.4 c.c. respectively during the two one-hour periods immediately following. During the next four hours the urine-forming function was practically suspended, as is shown by the formation of only 0.9 c.c. of urine. The specific gravity of the various fractions of urine ranged from 1.028 to 1.057. This high specific gravity was due in part to the presence of dextrose, inasmuch as glycosuria accompanied the anesthesia. Analysis of a composite sample of urine showed the presence of 5.29 per cent of dextrose. Our other data on the glycosuria following ether anesthesia have been presented elsewhere in this journal.

**TABLE 1.—URINE FORMATION DURING ANESTHESIA.** (Experiment 12.)

Hour	Length of Time after Anesthesia	Fraction	Total	Gravity
1	0-1	1.9	1.9	1.030
2	1-2	4.1	4.1	1.030
3	2-3	2.4	2.4	1.036
4	3-4	5.7	5.7	1.028
5	4-5	4.1	4.1	1.057
6	5-6	2.4	2.4	1.040
7	6-7	0.9	0.9	1.030
8	7-8	0.9	0.9	1.030

\*Cannulas in ureters and ether narcosis induced for ten hours and twenty minutes.

The second series of urine formation studies (Experiment 13) was made on Dog 3, a male weighing about 8.5 kg. The data are given in Table 2. The period of anesthesia was eleven hours and four minutes in length. In this experiment 55 c.c. of urine were collected during the operation. The first fraction collected from the ureter was one of 1.9 c.c. which was completed in an hour and three quarters after the induction of anesthesia. The data in this regard from Experiments 12 and 13 are very similar, in that the same volume of urine was formed during very similar periods of time. The maximum urine formation occurred between the second and third hours of anesthesia in this experiment, as against a fourth-fifth hour maximum in the case of Dog 1.

From the point of anax (anox) formation and some what regular decrease was observed while the hourly urine formation, indicating a gradual diminution of this function as given in the fractions collected between the various and elements of the various of the various were 0.2 cc and 0.2 cc in volume respectively. No urine was formed during the last half of the hour. The total volume of urine formed by this animal in a period of eleven hours and fourteen minutes was 20.7 cc as against 19.5 cc in the previous experiment on a similar interval of ten hours and twenty minutes. The specific gravity of the urine fractions varied from 1.020 to 1.050. The animal was also fed during this period of time with a sample of the analysis which was given in the previous paper as shown in the following table.

TABLE 2—RATE OF URINE FORMATION UNDER ETHER ANESTHESIA

Fraction No.	Hour	Collected		Length of		Total		Specific Gravity
		Time	Volume	Time	Volume	Time	Volume	
1	10 30 a m	1	1.5	1	1.5	1	1.5	1020
2	12 00 m	1	1.9	1	1.9	1	1.9	1022
3	12 30 p m	2	2.2	2	2.2	2	2.2	1025
4	1 00 p m	2	2.4	2	2.4	2	2.4	1025
5	2 00 p m	3	3.1	3	3.1	3	3.1	1044
6	3 00 p m	4	4.4	4	4.4	4	4.4	1046
7	4 00 p m	6	6.0	6	6.0	6	6.0	1050
8	5 00 p m	6	6.0	6	6.0	6	6.0	1050
9	6 00 p m	7	7.0	7	7.0	7	7.0	1050
10	7 00 p m	9	9.0	9	9.0	9	9.0	1050
11	8 00 p m	9	9.0	9	9.0	9	9.0	1050
12	9 00 p m	10	10.0	10	10.0	10	10.0	1050
13	9 30 p m	11	11.0	11	11.0	11	11.0	1050

\* Cannulas in ureters and ether narcosis induced for eleven hours and four minutes. The urine formation was 1.5 cc in the first hour and 1.5 cc in the second hour.

† Removed from cannulas at end of experiment.

‡ The third experiment of this series (Experiment 14) was made on a

dog weighing about 6.5 kg. The time of anesthesia was twelve hours

and twenty-four minutes. This experiment was marked by an almost

complete suppression of urine formation throughout the period of anes-

thesia. Only 3 cc of urine were formed in over twelve hours. The

first fraction (0.9 cc) was collected about four hours after anesthesia

had been induced, thus indicating the actual formation of 2.6 cc of

urine during this interval when the capacity of the cannulas is taken into

account. During the following hour 0.4 cc of urine was formed, but

The rectal temperature of this animal (Dog 5) was taken after eleven hours under ether and found to be  $23^{\circ}$  C or  $15^{\circ}$  below normal. This observation is right in line with similar findings by Simpson<sup>3</sup> in experiments on monkeys. In Simpson's experiments, however, the animal was placed in a cold chamber having a temperature of  $8.8^{\circ}$  C, whereas in our tests the animal was at room temperature. In one instance a reduction of body temperature to  $14^{\circ}$  C was observed by Simpson, this lowering of body temperature being followed by complete recovery, whereas in another instance a reduction to  $12.5^{\circ}$  C caused the death of the animal. The paralysis of the heat-regulating mechanism, under the influence of ether, as shown in these experiments on dogs and monkeys, is of considerable interest.

TABLE 3—RATE OF URINE FORMATION UNDER ETHER ANESTHESIA  
(Dog 5, EXPERIMENT 14)\*

Fraction No	Collected		Volume		Specific Gravity of Fraction
	Hour	Length of Time after Induction of Anesthesia	Fraction	Total	
	p m	hrs min	cc	cc	
1	1 10	3 4	0.9†		1050
2	2 15	4 9	0.4	1.3	1055
3	10 30	12 24	1.7‡	3.0	1068

\*Cannulas in ureters and ether narcosis induced for twelve hours and twenty-four minutes.

†This urine was collected entirely from the right kidney.

‡Removed from cannulas at end of experiment.

When we compare the data from the three experiments on urine formation, we find that two of them present very similar conditions. In Experiment 12, as well as in Experiment 13, the urine-formation was most rapid during the first portion of the anesthesia period. For example, in Experiment 12, in which the period of narcosis was ten hours and twenty minutes, the maximum urine flow occurred between the fourth and fifth hours, whereas in Experiment 13, in which the period of anesthesia was eleven hours and fourteen minutes, the maximum output was secured between the second and third hours. These two experiments are similar also in that the point of maximum urine formation was followed by a gradual inhibition of the urine-forming function which finally resulted in the practical cessation of all flow. The two experiments under comparison are closely comparable from the standpoint of the volume of urine formed during the anesthesia periods. The data indicate that in the first experiment 19.7 cc of urine were formed in ten hours and twenty minutes, whereas in the second experiment 20.7 cc of urine were formed in eleven hours and fourteen minutes. In other words, in one instance an

3 Simpson Jour Physiol, 1902, xxviii, Proceedings p 37



average of 1 c c of urine was formed every 32.5 minutes, whereas in the other instance a similar volume of urine was formed in 31.9 minutes.

When we consider the data from Experiment 14, it is at once apparent that there are few points of similarity between this experiment and the two experiments just discussed. The main point of similarity is found in the fact that the most rapid urine formation took place during the early hours of anesthesia. It will also be observed, however, that the total volume of urine formed during the experiment (3 c c) was only 15 per cent as great as that formed in Experiment 12 and only 14 per cent as great as that formed in Experiment 13. This is particularly surprising when it is remembered that the length of the anesthesia period was twelve hours and twenty-four minutes, an interval about two hours longer than the anesthesia period of Experiment 12 and about one hour longer than that of Experiment 13. It took twice as long (ten minutes) to get the subject of Experiment 13 completely under the influence of the anesthetic as it did the subjects of the other tests.

Similar inhibitions of the urine-forming function to that observed by us have been reported by Kemp<sup>4</sup> in experiments on dogs and by Tait<sup>5</sup> in connection with certain surgical procedure in which ether was the anesthetic. Seelig<sup>6</sup> and Goll<sup>7</sup> have also observed the partial suppression of urine formation under the influence of ether anesthesia. Some experiments made by Professor Gies and myself during the investigation of external hemorrhage are also of interest in this connection.<sup>8</sup> In one experiment the animal (dog) was placed under ether anesthesia and cannulas inserted in the ureters and the left femoral artery. The normal course of the urine formation was then observed for one hour. The animal was then subjected to a hemorrhage in which blood equivalent to 3.14 per cent of the body weight of the animal was removed. The formation of urine gradually decreased as the blood was being withdrawn and one minute after the end of the hemorrhage the urine flow entirely ceased. In twenty minutes the flow began again. A second hemorrhage induced about three hours later was accompanied by the same features regarding urine flow. In other experiments the blood removed from the animal was defibrinated and returned. The return of this defibrinated blood was found to cause an immediate increase in the rate of urine formation, in some instances the rapidity of urine flow being greater than normal.

#### SUMMARY

Three experiments were made to study the rate of urine formation under ether anesthesia. Dogs were used as subjects, cannulas being

4 Kemp New York Med Jour, 1899, lxx, 732

5 Tait Brit Med Jour, 1880, ii, 845

6 Seelig Arch f exper Path u Pharmacol, 1904-05, lii, 481

7 Goll Ztschr f rat Med, 1854, iv, 78

8 Hawk and Gies Am Jour Physiol, 1904, vi, 228

inserted in the ureters and the volume of urine formed for periods of from ten hours and twenty minutes to twelve hours and twenty-four minutes observed

Two of the experiments yielded very similar data. In each instance the first portion of the period of narcosis witnessed the most rapid formation of urine, the maximum output occurring in one case between the second and third hours and in the other case between the fourth and fifth hours, the flow gradually decreasing in each instance from this point to the end of the experiment. The average excretion for each experiment was approximately 2 c c per hour.

The third experiment, although embracing the longest anesthesia period, was also marked by the smallest urine flow. Only 3 c c of urine were formed during twelve hours and twenty-four minutes of anesthesia, the flow being entirely suppressed during the last eight hours of this interval. Glycosuria was observed in each experiment.

A body temperature (rectal) of 33 C was observed in a dog after the animal had been subjected to the influence of ether anesthesia for a period of ten hours.

Taking the data from these experiments into consideration with the data from others already reported<sup>1</sup> it is apparent that ether anesthesia causes an inhibition of the urine-forming function during the time anesthesia is induced, but that such inhibition is quickly followed by a stimulated urine flow which is initiated as soon as the period of anesthesia terminates.

The inhibition of the urine-forming function was probably due to the effect of the ether in constricting the arterioles of the kidney's blood-supply. A contributing factor may have been the increased affinity of the tissue colloids for water brought about through the influence of the ether, thus leaving less water to be excreted through the kidneys.<sup>9</sup>

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<sup>9</sup> See Fischer's *Edema*, 1910, p. 194.

# THE LABORATORY DIAGNOSIS OF GENERAL PARESIS

JAMES V. MAY, M.D.

BINGHAMTON, N. Y.

During the past year an investigation has been made in the laboratory of the Binghamton State Hospital for the Insane, of the cerebrospinal fluid from fifty-seven patients with general paresis, for the purpose of determining the relative value of the various laboratory methods of diagnosis which are now in quite general use. The results are shown in Table 1. As a control the same tests were applied to the spinal fluid from twenty-nine patients unquestionably suffering from psychoses other than general paresis. The fluids were obtained by lumbar puncture, about 10 c.c. being removed as a rule. The patients were kept in bed for twenty-four hours after the operation and no dangerous results occurred. Headache, dizziness, backache, and sometimes nausea followed, but no more severe symptoms were noted. The spinal fluid in general paresis is clear in appearance in the great majority of cases and when not, the cloudiness is nearly always due to blood caused by the needle, and not present in the fluid, as shown by subsequent autopsy, although cloudy fluid may be found when the autopsy is not performed soon after death. Rarely is it cloudy during life in cases which are characterized by an unusual increase in the number of cells.

The reaction of the fluid is very faintly alkaline, as shown by litmus paper, and is practically constant in normal as well as pathological fluids. The slight variations in disease are not of diagnostic value, and no effort was made to determine the exact degree of alkalinity which is usually stated as corresponding to 0.1 per cent of sodium hydrate.

Methods of estimating the pressure of the cerebrospinal fluid are unreliable and have not proved satisfactory. It is sometimes estimated by the number of drops per minute. Obviously this depends largely on the lumen of the needle used. The estimation of pressure by a water or mercury manometer is difficult and unnecessary. The various factors which influence pressure are so numerous as to render it of no value in diagnosis. The variations as stated in the tables shown here merely signify that the rate and force of flow from the needle was apparently greater or less than that observed in the average case not suffering from general paresis. The pressure shows no appreciable difference in many instances after death, the fluid flowing as freely as during life when the body is placed in the same position. In the fifty-seven cases of general

paresis examined the pressure seemed to be increased in twenty-seven cases, decreased in fifteen, and in fifteen it showed no apparent difference from that found in other forms of insanity

Serum-albumin is usually considered as being absent in normal spinal fluid although it shows a slight cloud on heating and gives a decided ring with the nitric acid and nitro-magnesium contact tests in all cases. The latter method, in which the fluid is brought into contact in a pipette with a mixture of 25 parts of nitric acid and 75 parts of saturated solution of magnesium sulphate, is much the more delicate. These reactions are merely due to proteins and are not to be looked on as an indication of the presence of albumin. The quantitative estimation of the protein content is unsatisfactory. The Esbach albuminometer is the instrument commonly used. The amount of fluid necessary for the determination can be diminished by diluting with distilled water and allowing for the dilution in computing the result. Reference to Table 2 will show that twenty-two out of twenty-nine cases (not cases of general paresis) or 75 per cent of the total number show from 0.03 to 0.06 per cent of protein by the Esbach method. The amount of protein in normal spinal fluid is given by Mott as 0.03 per cent. In the cases of general paresis Table 1 will show that forty-four of the fifty-seven cases, or 77 per cent, gave over 0.06 per cent, and twenty-nine over 0.1 per cent of protein by the Esbach albuminometer. This would seem to be an important although a slow method of diagnosis unless the centrifuge is used.

It will be observed that sugar was found in practically all cases without any reference to the form of insanity. It is now conceded by Halliburton to be present in normal fluid and is said to occur in smaller quantities in dementia præcox. The amount of fluid necessary for a quantitative examination renders it impracticable for diagnostic purposes. In the last annual report of the Binghamton (New York) State Hospital,<sup>1</sup> attention was called to the interesting fact that sugar is usually absent in post-mortem spinal fluid.

In all cases of general paresis a considerable excess of globulin is found in the cerebrospinal fluid. This is usually readily demonstrated by the butyric acid test of Noguchi. Two parts of spinal fluid are heated to the boiling point with five parts of a 10 per cent solution of butyric acid in either distilled water or 0.9 per cent salt solution after which one part of normal sodium hydrate solution is added and the mixture again boiled. The appearance of a flocculent precipitate within two hours is considered by Noguchi as diagnostic of general paresis. Blood-free fluid must be used. All spinal fluid contains globulin and in normal fluids or fluid from cases other than general paresis a flocculent precipitate may be obtained nearly always either by reboiling once or twice or allowing the

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1 Thirty First Ann. Rep. Binghamton State Hospital, Binghamton, N. Y., 1910, J. B. Lyon Co., Albany, p. 31.

mixture to stand for twenty-four hours. Usually boiling for a second or third time after the fluid has once cooled without allowing the fluid to stand, will bring down a flocculent precipitate in cases which show no evidences of general paresis.

Positive results were obtained by one or the other of these methods in twenty-seven out of twenty-nine non-paretic cases. In some of these fluids the precipitate occurred as quickly as in general paresis and after one heating only. Reference to Table 2 will show that sixteen out of twenty-nine non-paretic cases, 55 per cent of the total, gave positive results with the butyric acid reaction when the technic of Noguchi was employed. Rosanoff and Wiseman<sup>2</sup> in psychoses other than general paresis, obtained positive results with the butyric acid method in 10.8 per cent and doubtful reactions in 7.2 per cent of the 333 cases, making a total of 18 per cent which failed to give definite negative reactions. The technic of Noguchi was followed in these tests.

Dr F W Mott,<sup>3</sup> F R C P, London, F R S, pathologist to the London County Asylums, in his Oliver-Sharpey lectures on the cerebrospinal fluid delivered before the Royal College of Physicians of London on April 22 and 29, 1910, says of the butyric acid reaction of Noguchi: "I have applied this test to a considerable number of fluids, and have obtained a positive reaction in many non-specific cases, in fact, in all cases of dementia, whether non-specific or specific, and have found that the amount of precipitate is proportional to the degree of degeneration of nervous tissue, being most marked in the progressive degeneration of general paralysis of the insane."

Attention was called to the fallacy of this reaction in the last annual report of the Binghamton State Hospital<sup>4</sup> and also to the fact that it could be easily demonstrated by using larger amounts of the various reagents concerned than are recommended by Noguchi,<sup>5</sup> preserving, however, the same proportions (0.5 c c of spinal fluid, 2.5 c c of the 10 per cent butyric acid solution and 0.5 c c of normal sodium hydrate instead of 0.1 c c of spinal fluid, 0.5 c c of 10 per cent butyric acid and 0.1 c c of normal sodium hydroxid). "It is entirely to one's individual taste whether one or a multiple of the quantities indicated above will have to be employed."

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2 Rosanoff, A J, and Wiseman, J I. Syphilis in Insanity, *Am Jour Insan*, 1910, lxi, 430.

3 Mott, F W. Oliver-Sharpey Lectures on the Cerebrospinal Fluid, *Lancet*, London, 1910, ii, 79.

4 Thirty-First Ann Rep Binghamton State Hospital, p 32.

5 Noguchi, H. Relation of Protein, Lipoids, and Salts to the Wassermann Reaction, *Jour Exper Med*, 1909, ii, 92.

W H Hough<sup>6</sup> of Washington, D C, says of the butyric acid reaction

I found it positive, and in some instances very pronounced, in a number of cases of arteriosclerotic dementia where no evidence of syphilitic or inflammatory disease could be found, either in the cytology of the fluid or in the histological examination of the nervous system in the cases in which autopsy could be performed It may be mentioned also that a large majority of the post-mortem fluids from non-inflammatory cases showed a positive butyric acid reaction

He reports positive results in 48 per cent of his non-paretic cases and obtained five positive results in seven post-mortem fluids He followed the technic of Noguchi throughout It is beyond dispute that there is an increase of the globulin content in the spinal fluid in cases of general paresis, although it occurs in other psychoses as well and is not absolutely diagnostic of that disease<sup>7</sup>

The demonstration of an increase in the globulin content suggested the Nonne-Jones reaction, which has also been spoken of as valuable in the diagnosis of general paresis This reaction consists in the formation of a white ring such as is obtained in Heller's test for albumin on bringing spinal fluid in contact with a saturated solution of neutral ammonium sulphate solution in a pipette In the laboratory of the Binghamton State Hospital we have obtained positive results uniformly in general paresis but have had the same experience as shown in Table 2 with the spinal fluid in other psychoses If a white ring does not form immediately at the point of contact, it will form almost always after standing for a short time When there is any doubt as to the result a larger amount of fluid can be used and the reaction performed in a test-tube Positive results will be obtained in this manner from practically all spinal fluids In this as in all of the contact tests, a more decided reaction is, however, obtained in general paresis No reference is made here to the results obtained by the so-called precipitate reactions with lecithin and the taurocholate and glycocholate of sodium, owing to the fact that these reactions have already been shown to be unreliable<sup>4</sup>

One of the most valuable of the laboratory methods of diagnosis of general paresis consists in the demonstration of a lymphocytosis in the spinal fluid The method probably most often used is the old method of Widal and Ravaut, that of centrifuging the fluid and examining the sediment for an increase in the number of lymphocytes This is an easy and fairly accurate method We have found, however that a moderate

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<sup>6</sup> Hough W H Remarks on the Comparative Diagnostic Value of the Noguchi Butyric Acid Reaction and Cytological Examination of the Cerebrospinal Fluid Bull 2, Government Hospital for the Insane, Washington, D C, 1910, p 122

<sup>7</sup> May, J V A Review of the Recent Studies of General Paresis, 1909 Tr Am Med Psychol Assn Lord Baltimore Press Baltimore Md vii 317

increase of lymphocytes will occasionally be overlooked. Much more reliable is the accurate estimation of the number of cells per cubic millimeter of fluid by means of the Fuchs-Rosenthal counting chamber. In this method the pipette usually employed in counting the white blood cells is used.

The following mixture is usually employed for staining the white and dissolving the red cells. Methyl violet 0.2, glacial acetic acid 1, water 100. Fill the pipette with stain to the point marked 1 and then fill to the point marked 11 with cerebrospinal fluid, uncentrifuged. Shake thoroughly, let stand for five minutes and count by means of the Fuchs-Rosenthal counting chamber. The ruled surface of the cell contains 32 cubic mm of the fluid. Count all of the white cells in the entire ruled area of the slide, multiply by 11 and divide by 32. The result is the number of cells per cubic millimeter.

As the chamber is 0.2 mm deep the source of error can be entirely disregarded.

This method requires a very short time, after a little experience, and is quite reliable. The stain can be greatly improved by increasing the amount of glacial acetic acid used. Polychrome methylene-blue is recommended by Cornell. The spinal fluid should be free from blood, although a small amount does not materially affect the result. Reference to Table 2 will show that in twenty-five out of twenty-eight of the non-paretic cases there were five cells or less per cubic millimeter. On the other hand, in the forty cases of general paresis in which cell counts were made as shown in Table 1, only one case showed less than five cells to the cubic millimeter, while eight cases showed from five to twenty-five cells, twelve cases from twenty-five to fifty cells, fourteen cases from fifty to 100 cells, two cases from 100 to 200 cells, and three cases over 200 cells, per cubic millimeter. In our hands this method has constituted the most reliable laboratory procedure available in the diagnosis of general paresis. It will frequently show a considerable increase in the number of cells when the Widal-Ravaut method gives negative results.

Whenever a lymphocytosis is shown, a differential count of the cells should be made by the Alzheimer method, as follows:

Mix five c.c. of the spinal fluid with 10 c.c. of 95 per cent alcohol and centrifuge for one hour. Pour off the alcohol and replace by absolute alcohol. After standing for one hour replace by equal parts of absolute alcohol and xylene followed by xylene for one hour and imbed the sediment in paraffin by the usual process. Sections should be at least 12 microns thick and stained by 1 per cent toluidin blue and by the Unna-Pappenheim stain. At least 100 cells should be counted and the percentage of lymphocytes, polynuclears, large mononuclears, macrophages, *Körnchenzellen*, plasma cells, endothelial cells, etc., carefully estimated.

There will usually be found to be about 80 per cent of lymphocytes and from 1 to 5 per cent of plasma cells, with varying percentages of the other elements in cases of general paresis. The great increase of phagocytic cells and *Körnchenzellen* or fatty granule cells in all post-

TABLE 1—GENERAL PARESIS

Case No	General Characteristics *		Cerebrospinal Fluid								Blood Serum		
			Estimation of Globulin and other Proteins					Sugar Determination	Estimation of Cellular Elements	Test for Antibodies	Tests for Antibodies		
	Appearance	Pressure	Nitric Acid Contact Test	Nitro-Magnesium Contact Test	Esbach Albuminometer, Per Cent	Nonne Jones Contact Test	Butyric Acid Test	Fehling Qualitative Test	Widal Method	Fuchs - Rosenthal Cell Count Meth	Noguchi - Wassermann Reaction	Noguchi - Wassermann Reaction	Wassermann Reaction
1	++		++	++	3	++	++	++	++		++	++	+
2	++		++	++	15	++	++	++	++		++	++	++
3	++		++	++	09	++	++	++	++	272	++	++	++
4	++		++	++	12	++	++	++	++	36	++	++	++
5	++		++	++	07	++	++	++	++	4	++	++	++
6	++		++	++	12	++	++	++	++		++	++	++
7	++		++	++	15	++	++	++	++	32	++	++	++
8	++		++	++	07	++	++	++	++		++	++	++
9	++		++	++	12	++	++	++	++		++	++	++
10	++		++	++	21	++	++	++	++	8	++	++	++
11	++		++	++	12	++	++	++	++		++	++	++
12	++		++	++	12	++	++	++	++		++	++	++
13	++		++	++	09	++	++	++	++	89	++	++	++
14	++		++	++	12	++	++	++	++		++	++	++
15	++		++	++	04	++	++	++	++	93	++	++	++
16	++		++	++	12	++	++	++	++	273	++	++	++
17	++		++	++	21	++	++	++	++	32	++	++	++
18	++		++	++	12	++	++	++	++		++	++	++
19	++		++	++	06	++	++	++	++	9	++	++	++
20	++		++	++	09	++	++	++	++	54	++	++	++
21	++		++	++	12	++	++	++	++	30	++	++	++
22	++		++	++	04	++	++	++	++		++	++	++
23	++		++	++	06	++	++	++	++	35	++	++	++
24	++		++	++	09	++	++	++	++		++	++	++
25	++		++	++	12	++	++	++	++		++	++	++
26	++		++	++	18	++	++	++	++	89	++	++	++
27	++		++	++	07	++	++	++	++	68	++	++	++
28	++		++	++	12	++	++	++	++		++	++	++
29	++		++	++	09	++	++	++	++		++	++	++
30	++		++	++	18	++	++	++	++		++	++	++
31	++		++	++	07	++	++	++	++		++	++	++
32	++		++	++	09	++	++	++	++		++	++	++
33	++		++	++	15	++	++	++	++	203	++	++	++
34	++		++	++	15	++	++	++	++	36	++	++	++
35	++		++	++	25	++	++	++	++	46	++	++	++
36	++		++	++	12	++	++	++	++	30	++	++	++
37	++		++	++	12	++	++	++	++	61	++	++	++
38	++		++	++	06	++	++	++	++	19	++	++	++
39	++		++	++	12	++	++	++	++	39	++	++	++
40	++		++	++	12	++	++	++	++	66	++	++	++
41	++		++	++	09	++	++	++	++	108	++	++	++
42	++		++	++	06	++	++	++	++	65	++	++	++
43	++		++	++	09	++	++	++	++	22	++	++	++
44	++		++	++	06	++	++	++	++	20	++	++	++
45	++		++	++	12	++	++	++	++	42	++	++	++
46	++		++	++	06	++	++	++	++	80	++	++	++
47	++		++	++	12	++	++	++	++	27	++	++	++
48	++		++	++	06	++	++	++	++	7	++	++	++
49	++		++	++	04	++	++	++	++	46	++	++	++
50	++		++	++	03	++	++	++	++	22	++	++	++
51	++		++	++	06	++	++	++	++	69	++	++	++
52	++		++	++	09	++	++	++	++	95	++	++	++
53	++		++	++	09	++	++	++	++	58	++	++	++
54	++		++	++	06	++	++	++	++	18	++	++	++
55	++		++	++	15	++	++	++	++	72	++	++	++
56	++		++	++	09	++	++	++	++	118	++	++	++
57	++		++	++	12	++	++	++	++	84	++	++	++

• Reaction alkaline throughout

† Clear

‡ Cloudy

&lt; Decreased

&gt; Increased

= Normal



mortem fluids is of considerable interest. A lymphocytosis is not of course absolutely diagnostic of general paresis and occurs in cerebrospinal syphilis as well as in some cases of locomotor ataxia and tubercular meningitis.

TABLE 2—PSYCHOSES OTHER THAN GENERAL PARESIS

Case Number	Cerebrospinal Fluid										Blood Serum	Diagnosis Form of Psychosis	Deteriora- tion	History of Syphilis	
	Pressure	General Char- acteristics*	Estimation of Glob- ulin and other Proteins					Sugar Deter- mination	Estimation of Cellular Ele- ments						Test for Anti- bodies
			Nitric Acid Con- tact Test	Nitro-Magnesium Contact Test	Esbach Albumino- meter Per Cent	Nonne-Jones Con- tact Test	Butyric Acid Test	Fehling Qualita- tive Test	Widal Method	Fuchs - Rosenthal Cell Count Meth	Noguchi - Wasser- mann Reaction				Noguchi - Wasser- mann Reaction
1			++	++	03	++	—	—	—	1	—	—	Dementia præcox	Advanced	—
2	^^	^^	++	++	06	++	—	—	—	5	—	—	Alcoholic psychosis	Slight	++
3	^^	^^	++	++	09	++	++	++	++	1	—	+	Locomotor ataxia	Slight	++
4	^^	^^	++	++	04	++	—	—	—	1	—	—	Glioma of brain	Advanced	—
5	^^	^^	++	++	07	++	++	++	—	2	+	+	Locomotor ataxia	Advanced	—
6	^^	^^	++	++	05	++	++	++	—	3	—	—	Dementia præcox	Advanced	—
7	^^	^^	++	++	06	++	++	++	—	3	—	—	Dementia præcox	Advanced	—
8	^^	^^	++	++	03	++	++	++	—	1	—	—	Dementia præcox	Advanced	—
9	^^	^^	++	++	03	++	++	++	—	3	—	—	Dementia præcox	Advanced	—
10	^^	^^	++	++	13	++	++	++	—	3	—	+	Dementia præcox	Advanced	—
11	^^	^^	++	++	05	++	++	++	—	3	—	+	Dementia præcox	Advanced	—
12	^^	^^	++	++	06	++	++	++	—	2	—	—	Dementia præcox	Advanced	—
13	^^	^^	++	++	06	++	++	++	—	1	—	—	Dementia præcox	Advanced	—
14	^^	^^	++	++	06	++	++	++	—	3	—	+	Dementia præcox	Advanced	—
15	^^	^^	++	++	12	++	—	++	—	3	—	+	Dementia præcox	Advanced	—
16	^^	^^	++	++	04	++	—	++	—	3	—	+	Dementia præcox	Advanced	—
17	^^	^^	++	++	05	++	—	++	—	3	—	—	Dementia præcox	Advanced	—
18	^^	^^	++	++	05	++	+	++	—	1	—	—	Dementia præcox	Advanced	—
19	^^	^^	++	++	05	++	—	++	—	3	—	—	Dementia præcox	Advanced	—
20	^^	^^	++	++	06	++	—	++	—	3	—	+	Dementia præcox	Advanced	—
21	^^	^^	++	++	06	++	++	++	—	1	—	—	Dementia præcox	Advanced	—
22	^^	^^	++	++	03	++	—	++	—	2	—	—	Dementia præcox	Advanced	—
23	^^	^^	++	++	06	++	++	++	—	1	—	—	Dementia præcox	Advanced	—
24	^^	^^	++	++	09	++	—	++	—	2	—	—	Dementia præcox	Advanced	—
25	^^	^^	++	++	09	++	++	++	—	2	—	—	Dementia præcox	Advanced	—
26	^^	^^	++	++	05	++	++	++	—	3	—	—	Dementia præcox	Advanced	—
27	^^	^^	++	++	06	++	++	++	—	3	—	—	Dementia præcox	Advanced	—
28	^^	^^	++	++	06	++	—	++	—	7	—	+	Unclassified	Slight	—
29	^^	^^	++	++	09	++	—	++	—	5	—	+	Unclassified	Slight	+

\* Appearance clear and reaction alkaline throughout  
 < Decreased > Increased

= Normal

The Noguchi modification of the Wassermann reaction was used in the cerebrospinal fluid and in the blood-serum in both series of cases. In fifty-seven cases of general paresis the Noguchi method gave fifty-one positive reactions in the spinal fluid. In the other psychoses it gave only one positive in twenty-nine cases and that in a case of locomotor ataxia. In the blood-serum the Noguchi-Wassermann method gave positive reactions in all of the fifty-seven cases of general paresis, while in the twenty-nine cases of other psychoses it gave ten positive results. Of these ten cases two were cases of locomotor ataxia and one had a history of syphilis. In the other seven cases no history is available. The original Wassermann

reaction in the blood-serum of the general paresis cases gave thirty-eight positive results in forty cases and in the non-paralytic cases gave twenty-five negatives out of twenty-eight. Of the three positive reactions one was a case of locomotor ataxia. No reason can be assigned for the other two reactions. Both of these, however, were cases in which there was a reaction to the Noguchi modification. In comparing the two systems the Noguchi modification is by many looked on as being too sensitive and giving too many positive results in non-specific cases. This, however, as Noguchi suggests, may be due to the use of excessive amounts of antigen. In regard to the interpretation of results Noguchi<sup>8</sup> says

If there is a faint degree of hemolysis, the main bulk of corpuscles being intact, the reaction should be called positive. A more intense hemolysis, with about 10 to 20 per cent dissolution of the corpuscle mass, should be called weakly positive, while 30 to 40 per cent hemolysis is designated as faintly positive. Neither the weakly positive nor the faintly positive reaction should be accepted as a definite diagnosis of syphilis without the presence of strong clinical evidence in favor of such a diagnosis.

In another place he says <sup>9</sup>

It is my rule to base the diagnosis of syphilis on unmistakably strong reactions only, but never on weak reactions when the clinical diagnosis is unknown. On the other hand, I take even a faint positive reaction as a sign of active syphilitic process still present when the specimen is derived from a known luetic case. Again, for the purpose of excluding possibility of syphilis from a case I put value even on a faint reaction, no matter whether the person may seem healthy or not.

It will thus be seen that the result obtained is interpreted differently, depending on whether the case is one of known or probable syphilis, one showing no evidence or history of syphilis or one of which nothing is known unless there is practically a complete inhibition of hemolysis which does not always occur in many known syphilitic cases. In this way the personal equation enters strongly into the results obtained and the least inaccuracy in the amounts of the various factors concerned materially changes the results. The most serious objection to the Noguchi modification would appear to be the variability in the amount of specific ambocceptor contained in the capillary drop of blood-serum used. No two capillary drops from any two different tubes are the same. Negative results will sometimes be obtained from a capillary drop of blood-serum which will give positive results when from 0.02 to 0.04 c.c. are accurately measured from a graduated pipette for the test. According to Noguchi a capillary drop contains 0.02 c.c. of blood-serum. Measuring a few drops from different capillary tubes will readily convince anyone that

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<sup>8</sup> Noguchi, *Serum Diagnosis of Syphilis*, First Edition 1910, p. 61.

<sup>9</sup> Noguchi, II. Discussion of Serodiagnosis of Syphilis. *Jour. Am. Med. Assn.* 1909, III, 1541.

this is only occasionally true. Blowing out a few drops on a glass slide from capillary pipettes made from several different sizes of glass tubing will be sufficient to convince anyone that this is a very indefinite amount.

We have obtained very satisfactory results here from the use of the original Wassermann reaction. This method has the advantage of using a definite and easily and accurately measured amount of serum. It is quite unusual for blood to contain a sufficient amount of natural antishoop amboceptor to influence the result. Complement is completely removed by inactivation. We have not found the paper preparations of Noguchi to be stable or reliable for more than a few months although they are much more convenient to use than the liquid antigen and amboceptor. The amount of complement contained in guinea-pig serum is extremely variable and sometimes leads to erroneous conclusions. Only full-grown pigs should be used and a titration of the complement in the serum from a number of guinea-pigs will show that there is no absolutely invariable dose which can be depended on for use. We have found the following method of using the Wassermann reaction very satisfactory.

Patient's serum 0.2 c.c. or 0.1 c.c. (inactivated at 56 C for one half hour) plus 1 unit of antigen, plus 0.1 c.c. of guinea-pig complement undiluted, plus 2 c.c. of 0.85 per cent salt solution. Incubate for one hour at 37 C. Add 1 c.c. of a 5 per cent suspension of sheep corpuscles and 2 units of anti-sheep amboceptor. Incubate for two hours using the customary positive and negative controls.

The acetone-insoluble fraction of the alcoholic extract of human heart is used in the paper form. The antishoop amboceptor is also used in the paper form and both of these have been as satisfactory as the paper preparations used in the Noguchi modification.

An effort has been made to adopt the 'meiostagmin' reaction of Ascoli to the diagnosis of general paresis by using the cerebrospinal fluid and the alcoholic extract of human heart as antigen. Ascoli announced<sup>10</sup> that the addition of antigen of syphilis in varying dilutions to the serum of a person suffering from that disease brought about a considerable change in the surface tension of the fluid on standing for a time in the incubator. This change in tension is measured by a Traube stalagmometer. After numerous attempts we have been unable to obtain any uniform results with the serum of syphilitic cases.

#### CONCLUSIONS

1. There is an increase in the protein content of the cerebrospinal fluid in general paresis.

2. There is a marked increase in the globulin content in general paresis.

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<sup>10</sup> Ascoli, M. Die Spezifische Meiostagminreaktion, *Munch. Med. Wchnschr.*, 1910, lvi, 63.

3 There is an increase in the globulin content in psychoses other than general paresis in many cases

4 The increase in the globulin content can be shown better by using larger quantities of the reagents suggested by Noguchi for his butyric acid test, preserving, however, the same proportions This method will show an increase which would often be overlooked otherwise

5 The butyric acid test of Noguchi has not been accepted as absolutely diagnostic of general paresis

6 The demonstration of a lymphocytosis in the spinal fluid is one of the most reliable laboratory methods in the diagnosis of general paresis

7 In the performance of the Noguchi modification of the Wassermann reaction it is important to use a sufficient quantity of the serum to be tested, the capillary drop recommended by Noguchi being a very variable amount

8 The Noguchi method of interpreting the results of the Wassermann test differs largely from that of many other laboratory workers and may lead to various conclusions, depending on the observer

9 The original Wassermann method is to be preferred to the Noguchi modification

10 The Noguchi method of using antigen and amboceptor in the paper form can be adapted to the original Wassermann reaction with advantage

Binghamton State Hospital, Binghamton, N Y

# EDEMA OF THE PIA-ARACHNOID

ITS NATURE, SIGNIFICANCE, RELATIONSHIP TO AND ASSOCIATION WITH  
DISEASE PROCESSES \*

CHARLES K STILLMAN, M D  
NEW YORK

## INTRODUCTION

The following article is a study of the nature and significance of fluid accumulations within the subarachnoid space, based principally on post-mortem observations and mechanical considerations

For the sake of brevity it may be stated at the outset that the terminology employed to designate the various conditions of the brain and its membranes associated with excessive fluid accumulations has been confused by the use of many names, employed without due consideration of the etiological or mechanical factors involved. It is therefore necessary to describe the various anatomical findings to which these different terms have been applied

1 *Pial Edema, Edema of the Pia Mater, Edema of the Pia Arachnoid, Cerebral Edema, Wet-Brain*—These terms have been employed indefinitely to designate conditions accompanied by excess of fluid in the pia-arachnoid. The brain on cut section may or may not appear to be moist, the ventricles may or may not be "dilated." The volume of the brain is not increased, on the contrary it often has given the impression of having been compressed. It is this picture which is generally associated with and attributed to chronic alcoholism, and which in this country has often been referred to as wet-brain

2 *Cerebral Edema, Edema of the Brain*—Swelling of the brain with increase in its volume. The pia-arachnoid may or may not have contained an excess of fluid, usually the convolutions are described as flattened, owing, as supposed, to pressure of the voluminous brain against the skull. These brains are then described as being moist, the condition being usually attributed to transudation into the brain substance of serum from the blood-vessels

3 *Serous Meningitis*—Described usually as a serous or exudative inflammation of the soft meninges, with exudate into the subarachnoid space and its prolongations, with or without gross thickenings of the

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\*From the Pathological Laboratories of Bellevue Hospital, Dr Charles Norris, Director

meninges The ventricles may or may not be dilated and the brain is or is not secondarily involved, the seat of an edematous or inflammatory process Certain writers in this country, notably Dana, have regarded "alcoholic wet-brain" and serous meningitis as synonymous

4 *Hydrops ex Vacuo*—This term has been used to describe the accumulation of fluid following the shrinkage of the brain from old age or from various pathological causes, to be mentioned later

5 *Chronic External Hydrocephalus*—This term has been used to describe those appearances already referred to above, by some authors also, to describe accumulations of fluid in the subdural space and even those found between the calvarium and the dura mater <sup>1</sup>

The above summary, derived from a critical survey of the literature, shows that these various terms, although in themselves perfectly clear and descriptive, have been used indiscriminately to designate different anatomical conditions without any consideration of the underlying pathological processes in which they had their origin

Although the older writers did not formulate any noteworthy theories as to the causation of excessive accumulations of fluid in the brain,<sup>2</sup> they nevertheless displayed considerable interest in its supposed mechanical effects Thus we find in Watson's Lectures<sup>3</sup> (1845), the following rather quaint description of fluid collections in the pia-arachnoid in connection with uremic coma

Now when death had thus taken place in the way of coma and the case had been complicated with anasarca, and serous liquid is found accumulated in unnatural measure in the cerebral ventricles, and in the tissue of the pia mater, it seems reasonable to ascribe the coma to the presence and the pressure of that liquid The dropsy has extended to the brain And this view of the matter is strengthened by the connection which may sometimes be noticed between the accession of the coma and the visible increase of the dropsy in other parts of the body My own experience accords entirely with that of Dr Christison as expressed in the following statement "If the dropsical fluid be allowed greatly to accumulate, drowsiness, the first symptom of the affection of the head, very soon makes its appearance in the generality of cases and it will speedily pass to total coma if not controlled, but the removal of the dropsy will usually remove the drowsiness" To many cases, however, this explanation will not apply there being no morbid collection of water within the skull, nor any other appreciable change there, nor perhaps any dropsy elsewhere

The fluid collections described by Watson were doubtless that very common form of pial effusion with which this paper particularly has to do

In 1861, Traube<sup>4</sup> opened up a new vista in the field of intracranial mechanics by stating that the brain is often swollen and edematous in

1 Riva, E *Idrocephalo interno ed esterno*, Riv spec di fieniat, 1908, \\\IV, 207

2 Traube quotes Osborne as attributing the condition to an arachnitis

3 Watson, Thomas *Principles and Practice of Physics*, London, 1845

4 Traube, L *Eine Hypothese über den Zusammenhang, in welchem die sogenannten urämischen Anfälle zur Erkrankung der Nieren stehen*, Allg med Centr Ztg 1861, \\\ 318

certain cases of uremia Since Traube<sup>5</sup> may thus be regarded as the founder of a new school, a somewhat detailed consideration of his paper is imperative In discussing uremia he says "In all cases observed by me in which a careful examination of the cranial contents has been made after death, there was observed with a well-marked anemia [*Blut-Armuth*] of the brain, a more or less considerable edematous swelling of the same (as shown by flattening of the brain convolutions and dryness of the arachnoid, with moist glistening of the cut section)"<sup>6</sup> Further on he writes "In some of these cases the fresh petechiæ [*Blut-Ergüsse*] were distributed in the form of fine sand up to hemp-seed foci through the large and small brain and pons due," as he states, "to increased arterial pressure"<sup>7</sup> He lays especial stress upon two factors in the causation of brain edema in uremia, first, the hydremic condition of the blood, due to loss of albumin through the urine and through gastro-intestinal catarrh, and second, to the increased tension in the aortic system from hypertrophy of the left ventricle<sup>5</sup> He goes on to say

If through any accidental cause there occurs a sudden increase of blood-pressure, or if there is a sudden diminution in the thickness of the blood-serum, there transudes a serous fluid through the walls of the small arteries into the brain substance, and thus brain edema ensues The fluid elements of the blood transude under the mean pressure in the aortic system Since this pressure is greater than that in the capillaries and veins, so these vessels must finally be compressed The necessary consequence of a brain edema arising from such a cause is an anemia of the brain substance The transudation, as will be readily understood, resists up to the moment when the tension of the edematous brain parts equals the mean tension of the aortic system

Traube's explanation of the causes bringing about transudation is not generally accepted He cites a case of cerebral edema in an epileptic who at autopsy was found to have a cysto-sarcoma of the brain There is reason to believe that from this case he derived the idea on which he founded his theory as to the causation of the attacks of coma and convulsions occurring in cases of uremia and of chronic lead-poisoning

Several years after Traube's paper appeared, Billroth<sup>8</sup> (1869) observed anatomical changes in the brains of postoperative subjects somewhat similar to those described by Traube

Niemeyer<sup>9</sup> (1877) and Huguenin<sup>10</sup> (1878) reconsidered the problem chiefly in connection with the phenomena of uremia

5 Traube, L. *Gesammelte Beiträge zur Pathologie und Physiologie*, 11, Part 1, 551

6 Traube, L. *Gesammelte Beiträge zur Pathologie und Physiologie*, 11, Part 1, p 553

7 Traube, L. *Gesammelte Beiträge zur Pathologie und Physiologie*, 11, Part 1, p 554

8 Billroth. *Ueber akute Mening serosa und akute Gehirnodem nach chirurgischen Operationen*, Wien med Wchnschr, 1869, xix, 2

9 Niemeyer. *Lehrbuch der speziellen Pathologie und Therapie*, Ed 9, 1877, 11

10 Huguenin, G. *Hydrocephalus und Oedem des Hirns*, *Handbuch der speziellen Pathologie und Therapie von v Ziemssen*, Suppl Vol, 1878, p 25

Bergmann<sup>11</sup> (1880) described an edematous condition in connection with injuries of the brain, while Dean<sup>12</sup> produced local edema experimentally by placing a glass disc between the brain and the dura

Phelps<sup>13</sup> (1897) believes that edema of the brain may follow on concussion and W N Bullard<sup>14</sup> (1895) states that edema of the brain results from concussion The latter writes

Brain swelling undoubtedly occurs in certain cases of apoplexy, and in a chronic form in many intracranial diseases This, or something analogous to it, the so called acute edema of the brain, is the immediate cause of death in cases of acute alcoholism, of sunstroke and perhaps (in its chronic form) in uremia

Walton and Brooks<sup>16</sup> (1897) have also dwelt on the subject of edema of the brain and its membranes from a surgical standpoint Walton in his subsequent paper<sup>17</sup> has considerably modified his previous conceptions

W B Cannon<sup>18</sup> in an article published in 1901, presented certain striking and original conclusions on the causation of cerebral edema following trauma, which will be later referred to, while at about the same time Mott<sup>19</sup> succeeded in producing experimental edema of the brain in dogs by ligation of arteries, and Osler<sup>20</sup> (1901), following Traube, described cerebral edema particularly in connection with uremic coma

The subject of cerebral edema has aroused great attention among physiologists only within a comparatively recent period Wilson<sup>21</sup> (1904) studied the condition in connection with uremic and eclamptic seizures

11 Bergmann Die Lehre von den Kopfverletzungen, Deutsch Chm, Stuttgart, 1880, xxx, 420

12 Dean, H P Cerebrospinal Pressure, Jour Path and Bacteriol, 1893, 1, 26

13 Phelps, C Traumatic Injuries of the Brain and Its Membranes, New York, 1897, p 53

14 Bullard, W N A Consideration of Some of the Indications for Operation in Head Injuries, Med and Surg Rep, City Hosp, Boston, Series 6, 1895, p 60

15 Bullard, W N Increase of Intradural Pressure in Head Injuries, Boston Med and Surg Jour, 1898, cxxviii, 271

16 Walton, G L, and Brooks, W A Observations on Brain Surgery Suggested by a Case of Multiple Cerebral Hemorrhage, Boston Med and Surg Jour, 1897, cxxvii 301

17 Walton, G L Subarachnoid Serous Exudation Productive of Pressure Symptoms after Head Injuries, Am Jour Med Sc, 1898, cxvi, 267

18 Cannon, W B Cerebral Pressure Following Trauma, Am Jour Physiol, 1901, vi, 91

19 Mott, F W Preliminary Communication on the Changes in the Brain, Spinal Cord, Muscles and Other Organs Found in Persons Dying after Prolonged Epileptiform Convulsions, Arch Neurol, London, 1, 493

20 Osler, Wm Practice of Medicine, 1901, p 997

21 Willson, R N The Pathogenesis of Uremia and Eclampsia, Jour Am Med Assn, 1904, viii, 1019



B Bramwell<sup>22</sup> (1906) mentioned cerebral edema as a possible cause of uremic attacks. The following year A E Russell<sup>23</sup> (1907) introduced his thesis in the following terms: "The purpose of this paper is to put forward the proposition that there is evidence to show that the cerebral manifestations of uremia are dependent on cerebral anemia produced by an increase in intracranial tension resulting from cerebral edema." Following Russell, Cushing and Bordley<sup>24</sup> (1908) published a paper based chiefly upon the observations and findings ante and post mortem in a case of uremia in which decompression was performed, as a result of which he concludes: "In regard to uremia, therefore, to be conservative we may at least say that the symptoms are elicited by edema resulting from some toxic agency, and are not, as is commonly supposed, due to the direct effect on the cerebral tissues of the toxic agent alone."<sup>25</sup>

Russell<sup>26</sup> has very recently (1909) presented additional evidence supporting the hypothesis that the presence of edema of the brain is an important factor in the production of uremic phenomena. He says, speaking of Cushing's decompression case (mentioned above) and other recent data:

The foregoing facts indicate that in uremia a state of increased intracranial tension is present, and that relief of pressure by lumbar puncture or decompression causes a marked alleviation of the symptoms. Traube's view that cerebral edema (which would produce the rise in the intracranial tension) produces anemia of the brain is strongly supported by the above facts and especially by the striking case of decompression.

Russell does not deny a concomitant toxic action on the brain but thinks it possible that status epilepticus may be due to an anemia of the brain following on a prolonged increase of intracranial pressure. There is, as has been shown, a very strong tendency among the members of the Traube school to assume that the rise in intracranial tension is due to cerebral edema. As a matter of fact cerebral edema is a very inconsistent phenomenon in uremia, as has been noted not only by Russell but by Bramwell, and by a large number of authors who are not identified with

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22 Bramwell, B. Clinical Lecture on Uremia and its Treatment, Clinical Studies, Edinburgh, 1906, Part I, p. 1.

23 Russell, A. E. Uremia, West Lond Med Jour, 1907, xii, 9. This paper contains an excellent bibliography of the use of lumbar puncture in uremia.

24 Cushing, H., and Bordley, J., Jr. Subtemporal Decompression in a Case of Chronic Nephritis with Uremia, etc., Am Jour Med Sc, 1908, cxxvi, 484.

25 Cushing has dealt with the subject to a less extent in previous papers, See Am Jour Med Sc, 1903, cxxv, 1017.

26 Russell, A. E. The Gouldstonian Lectures on Some Disorders of the Cerebral Circulation and Their Clinical Manifestations, Lancet, London, 1909, i, 963, 1031, 1093.

27 Huguenin, Ibid.

the Traube school, namely, Huguennin, John Rose Bradford,<sup>28</sup> Senator<sup>29</sup> and Riesman<sup>30</sup>

In this connection the observations of Kolisko<sup>31</sup> on swollen and edematous brains, are most interesting. This observer has described a type of brain in which the brain is swollen and wet, the ventricles reduced in size and the fluid of the subarachnoid space diminished or absent, the convolutions flattened, associated with dural hernias, and marked *impressiones digitates*—the latter being due to a compression atrophy of the inner table of the skull described as following upon a premature ossification of the cranial sutures.

The clinical phenomena in these cases have not appeared to bear much resemblance to those recorded by the Traube school.

The term "serous meningitis," the etiological and anatomical status of which is intimately involved in any consideration of sub-arachnoid effusions, is of comparatively recent introduction, although its employment antedates the bacterial era of medicine.

Since the development of our subject depends chiefly on anatomical rather than general clinical considerations, we shall regard serous meningitis chiefly from the anatomical and mechanical point of view, and limit our review of it.

Among earlier writers it was usual to ascribe all cases of internal and external hydrocephalus to tuberculous meningitis, although certain observers, notable among whom were Dietl,<sup>32</sup> Rokitsansky,<sup>33</sup> Wunderlich<sup>34</sup> and Leubuscher<sup>35</sup> did not agree with this opinion.

In 1869 Billroth<sup>35</sup> distinguished a form of acute hydrocephalus of supposed non-tuberculous origin to which he applied the name of meningitis serosa. But it was not until Eichorst<sup>36</sup> (1887) published his observations that much emphasis was laid on the idea that a simple serous inflammation was the pathological process in many of these cases.

28 Bradford, John Rose. Observations on the Pathology of the Kidneys. Gouldstonian Lectures, Laneet, London, 1898, 1, 917.

29 Senator. Diseases of the Kidneys, Nothnagel's Encyclopedia, Am. Ed. p. 103.

30 An analysis of the fourteen autopsies on cases of uremic aphasia, quoted by Dr. D. Riesman, Uremic Aphasia, Jour. Am. Med. Assn., 1902, LVIII, 883 shows six in which there was moisture of the brain or edema. One had marked distention of the right ventricle and the remaining seven brains were described as normal.

31 Kolisko, Alexander. Plotzlicher Tod aus naturlicher Ursache, Handbuch der ärztlichen sachverständigen Tätigkeit. Vienna and Leipzig, 1906, II, 702 et seq.

32 Dietl. Anatomischer Klinik der Gehirnkrankheiten, 1846.

33 Rokitsansky. Lehrbuch der pathologischen Anatomie, 1856, II, Ed. 2.

34 Wunderlich. Die Pathologie und Therapie, 1854, III, Ed. 2.

35 Leubuscher. Die Pathologie und Therapie der Gehirnkrankheiten, Berlin 1854.

36 Eichorst. Handbuch der speziellen Pathologie und Therapie, 1887, III.

Eichorst believed that the process was due to a mild infection and remained serous throughout, while Gowers<sup>37</sup> (1892) described the process as a meningitis simplex as distinguished from a meningitis purulenta. He was followed shortly by Quincke<sup>38</sup> who elaborated a definite symptomatology for this disease.

The literature of serous meningitis has become so enormous that it is out of the question to attempt to review it, especially since Boenninghaus<sup>39</sup> has given a comprehensive summary of the subject up to 1897 and Hafslauer<sup>40</sup> has subsequently reviewed it up to 1906.

The subject did not receive much attention in the United States until Dana<sup>41</sup> (1897) published his article entitled "Acute Serous Meningitis (Alcoholic Meningitis, Wet-Brain)." Since then, articles, monographs or reports of cases bearing on the subject have appeared in this country by Lambert,<sup>42</sup> Smith,<sup>43</sup> West,<sup>44</sup> Gradle,<sup>45</sup> Stillman,<sup>46</sup> Fischer,<sup>47</sup> Diller,<sup>48</sup> Collins,<sup>49</sup> Tod,<sup>50</sup> Spiller<sup>51</sup> and Stein<sup>52</sup>, and abroad, either coincidentally with or since Hasslauer's summary by Verhoogen,<sup>53</sup> Hasslauer,<sup>54</sup> Blau,<sup>55</sup>

37 Gowers Diseases of the Nervous System, 1892, 11

38 Quincke Ueber Meningitis serosa, Samml klin Vortr, new series, No. 67, 1893, p 655 Also Ueber Meningitis serosa und verwandte Zustände, Deutsch Ztschr f Neuvenh, 1896, pp 149-168

39 Boenninghaus, G Die Meningitis serosa acuta, eine kritische Studie, Wiesbaden, 1897

40 Hafslauer Ueber Meningitis serosa, Sammelieferat internationales, Centralbl f Ohrenh, 1906, iv, Part 8, p 341

41 Dana, C L Med Rec, New York, 1897, lii, 801

42 Lambert, A Alcoholism, Osler's Modern Medicine, 1, 157, Bellevue Hosp Med and Surg Rep, 1904, 1, 113

43 Smith, E T Meningitis Serosa, Tr Am Otol Soc, New Bedford, Mass, 1907, x, 550

44 West, J P Serous or Posterior Basic Meningitis, Its Early Recognition and Treatment, Ohio State Med Jour, 1909, v, 323

45 Gradle, H A Case of Serous Meningitis, Jour Nerv and Ment Dis, 1906, xxxiii, 126

46 Stillman, C K Postdelirious Alcoholic Stupor, Alcoholic Cerebral Edema, (Wet-Brain), New York Med Jour, 1908, lxxvii, 154

47 Fischer, J S Serous Meningitis, Maryland Med Jour, 1908, li, 158

48 Diller A Case of Serous (Alcoholic) Meningitis Simulating Brain Tumor, Jour Nerv and Ment Dis, 1898, xxv, 441

49 Collins, J Diseases of the Meninges, Twentieth Century Practice of Medicine, N Y, 1897, x, 355

50 Tod, H Lateral Sinus Thrombosis, Subsequent Meningitis (Meningitis Serosa), Recovery, Otol, sec 30 32, Proc Roy Soc of Med, 1907-1908, 1, 30

51 Spiller, William G Circumscribed Serous Spinal Meningitis, Am Jour Med Sc, 1909, cxxlvii, 95

52 Stein, R Serous Meningitis in Typhoid Fever and Its Treatment by Lumbar Puncture, Am Jour Med Sc, 1910, cxxlix, 542

53 Verhoogen, R La méningite sereuse Jour d méd, Brux, 1907, xii, 111

54 Hafslauer Die bakteriologischen Befunde bei der eiterigen und serösen Meningitis mit besonderer Berücksichtigung die bei der Lumbalpunktion, etc, Internat Centralbl f Ohrenh, Leipsic, 1906-7, 1, 65

55 Blau, A A Case of Serous Meningo-Encephalitis with Autopsy Report, Ztschr f Ohrenh, 1906, lii, 129

Avellis,<sup>56</sup> Riebold,<sup>57</sup> Thiemich,<sup>58</sup> Paradis,<sup>59</sup> Aulhausen<sup>60</sup> and L Williams<sup>61</sup> A notable phase in the development of this subject of serous meningitis in the last few years has been the interest and attention which it has received from otologists

The etiology is so much in dispute and the descriptions of this process by various writers are so divergent, not only from the clinical but also from the anatomical standpoint, that it is impossible to define precisely what is meant by this term This state of affairs makes it also impracticable to dwell on the mechanical problems involved It is clearly out of the question to analyze the hundred or more articles which have appeared with this name for a subject

In general, however, it may be said that an external and an internal form of serous meningitis are recognized and that these may be acute or chronic In the acute external form the cortical pia arachnoid is described as being inflamed and infiltrated with round cells or leukocytes with serous exudation into the subarachnoid space and its prolongations Sometimes the adjacent brain tissue is inflamed and edematous When chronic, the pia may or may not be described as thickened In the internal form there is transudation into the ventricles with dilatation Quincke and others<sup>62</sup> have described the fluid as clear Boenninghaus<sup>63</sup> believes that acute idiopathic hydrocephalus follows acute serous meningitis, while Thiemich<sup>64</sup> apparently considers that the "so-called acute hydrocephalus of childhood" and "ventricular serous meningitis" are identical

Both Boenninghaus and Quincke have noted that non-inflammatory collections of fluid in the pia-arachnoid space are easy to mistake for serous meningitis These pial effusions were discussed by Huguennin many years previously He noted their association with certain atrophic states of the brain I consider that knowledge of the subject has not greatly advanced since Huguennin's time

Of late years much attention has been given to the abnormally large collections of fluid so often seen beneath the arachnoid membrane in

56 Avellis, G Oertliche Serosa Meningitis bei akuter Keilbemeiterung mit Spontanheilung, Verhandl d Ver sud deutsch Laryngol, 1907, 454

57 Riebold, G Ueber serosa Meningitis, Deutsch med Wehnsehr, 1906, XLII, 1859

58 Thiemich, M Serous Meningitis in Diseases of Children, Pfandler and Schlossman, Eng Trans, 1908, IV, 376

59 Paradis, A Ueber Meningitis serosa, B George, Leipsie, 1906, p 26

60 Aulhausen, G Zur Kenntniss der Meningitis serosa acuta Beil klin Wehnsehr, 1909, XLVI 244

61 Williams, L Serous Apoplexy, Med Press and Circular, 1906, LXXI, 499

62 Thiemich (Serous Meningitis in Diseases of Children, p 413) considers that the fluid of internal serous meningitis is usually clear but that there are slight changes which indicate inflammation of the choroid plexus and ependyma

63 Boenninghaus Die Meningitis serosa acuta, p 93

64 Thiemich Serous Meningitis, in Diseases of Children, p 415

subjects that have died of chronic alcoholism. It was primarily with the purpose of shedding some light on this subject that my paper was begun.

It became clear to me that post-mortem examinations of the brain alone would never throw sufficient light on the causation of these accumulations of fluid. I determined therefore to approach the subject by the following methods:

1. By means of an analysis of a series of cases, to show the frequency of association of pial edema with various diseases and to determine the influence of other factors such as age and nutrition.

2. By a consideration of the physical phenomena underlying the accumulation of fluid in the cranial cavity.

3. To determine whether there were any chemical differences in the cerebrospinal fluids in these various conditions that might indicate their etiological relation.

4. By the estimation and comparison of brain weights or volumes and cranial capacities in a series of cases.

With this brief introduction I now proceed to describe my observations.

#### *PART I ANALYSES OF CASES ACCORDING TO AGE, NUTRITION AND DISEASE*

Pial edema is a very common condition at autopsy, for out of a total of the 665 cases which form the basis of this report, it was recorded 375 times—a percentage of 56.4.

The cases with pial edema (375) have been placed in one group, those without pial edema in another.

##### *AGE*

An examination of the appended table shows. First, a relative frequency of pial effusion in infants from 4 months to 5 years of age.<sup>65</sup>

Second, an entire absence of this condition between the ages of 6 and 15 years, followed by a rapid increase that culminates between the thirty-fifth and fortieth years with later a more gradual increase that reaches the maximum at from 80 to 85 years (old age).

The youngest subject with pial edema was 4 months old. When it is observed that in this series there were fully thirty-one cases of children, between birth and the fourth month, with dry pias, this initial date may not be without some significance.<sup>66</sup> The absence of pial edema in nine subjects between 6 and 15 is also significant.<sup>67</sup>

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<sup>65</sup> Eighty-two infants were examined, of these eighteen presented pial effusion that is 21.9 per cent of the total number of cases.

<sup>66</sup> The ages of the thirty-one children mentioned above were as follows: 13 hours, 20 hours, 2½ days, 13 days, 21 days, 1 month (three cases), 6 weeks (two cases), 7 weeks, 2 months (nine cases), 9 weeks, 10 weeks, 3 months (nine cases).

<sup>67</sup> A case of marked pial edema in a boy of 15 who died of juvenile priapism was observed subsequently. In this case the brain shrinkage is readily explainable on pathological grounds.

In the examination of fourteen cadavers between the ages of 16 and 20 years, pial edema was found twice, or in 14.2 per cent.

In an examination of thirty-four cadavers between the ages of 21 and 25, 26.4 per cent presented pial edema. Of the nine, five showed a slight degree, three a moderate degree including one case of alcoholism, and one a marked degree (a case of cerebral syphilis).

In forty-five subjects between the ages of 26 and 30 years, 51.1 per cent, or twenty-three presented pial edema, five slight, nine moderate (including two alcoholics) and nine marked cases. It is important to note that in the nine marked cases, six subjects had lesions usually accompanied by brain shrinkage.

In sixty-four cases between the ages of 31 and 35 years forty cases showed pial edema, twenty moderate, twelve marked, and one extreme.

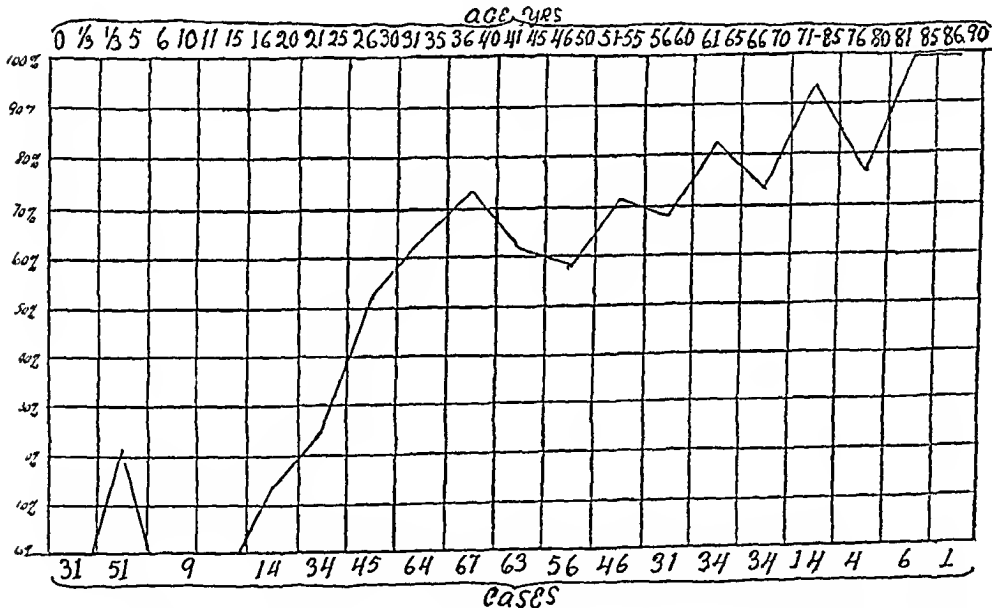


Fig 1—Chart, compiled from 604 cases, showing relative frequency of pial edema at various ages.

(including eight alcoholics and one case of insanity). The cause of death in the "extreme" case could not be determined.

In sixty-three subjects between the ages of 41 and 45 years, 61.9 per cent, or forty-one showed pial edema, twenty-one of moderate, eleven of marked and two of extreme grade, including in all six alcoholics.

In fifty-six subjects between the ages of 46 and 50 years, 58.9 per cent, or thirty-three, showed pial edema, twelve of moderate and eighteen of marked grade, including four alcoholics.

In forty-six subjects between the ages of 51 and 55 years 71.7 per cent, or thirty-three, showed pial edema, thirteen moderate, seventeen marked, one extreme (pulmonary tuberculosis). This group included two cases of chronic alcoholism and one of insanity.

In thirty-one subjects between the ages of 56 and 60 years, twenty-one, or 67·7 per cent, showed pial edema, eight moderate, nine marked and one extreme

In thirty-four cadavers between the ages of 61 and 65, 82·5 per cent, or twenty-eight, showed pial edema, nine moderate, eleven marked and three extreme cases, one case of alcoholism

In fourteen subjects between the ages of 71 and 75 years, 92·8 per cent, or thirteen, showed pial edema, six moderately and four markedly

The four subjects between the ages of 76 and 80 years, 75 per cent, or three, showed pial edema, all markedly. The brain of the subject without edema was normal in size and appearance

In six subjects between 81 and 85 years of age, 100 per cent showed pial edema, two moderately, two markedly, and two extremely

There was one subject showing pial edema between the ages of 85 and 90 years

#### NUTRITION

In neither adults or children did there appear to be any definite relation between pial edema and emaciation

Of 357 cases of pial edema in adults, forty-nine were not fully described as regards nutrition and therefore were subtracted from the general total, leaving 308 cases for analytical purposes. The state of nutrition in these cases of pial edema was as follows

Fat	14, or 4·5 per cent
Fair to good nutrition	168, or 54 per cent
Poorly nourished	34, or 11 per cent
Emaciated	64, or 20·7 per cent
Markedly emaciated	28, or 9 per cent

From the above it is seen that pial edema is associated with good nutrition in the majority of instances, (59 per cent as against 41 per cent for the badly nourished)

Of the eighteen infants who had pial edema, two were not fully described as regards nutrition. The remaining sixteen presented findings similar to those of the adult series given above. The nutrition in these cases was as follows

Fat	1
Well nourished	6
Poorly nourished	1
Emaciated	6
Much emaciated	2

The question whether all poorly nourished people have pial edema is answered by referring to the data concerning the cases in my series with dry pias. In this group cachexia was present ninety-eight times unassociated with any subarachnoidal collections of fluid—a number sufficiently large to show that no relationship exists between the two conditions

RELATIONSHIP BETWEEN PIAL AND EDEMA DISEASE PROCESSES<sup>68</sup>

The records were grouped according to the anatomical diagnosis with a view of determining whether any diseases or conditions were regularly associated with pial edema.

Pial edema is found on the average in practically two out of every three adults at autopsy. In our series of 542 adults, the subjects with pial edema, 355 in number, constituted 65.5 per cent of the total number. Those without pial edema, 187 in number, comprised 34.5 per cent of all the subjects.

It is evident that pial edema cannot be assumed to be related to any particular disease process unless it can be shown that it occurs with greater frequency with that disease than it does with other diseases. The simplest method to determine whether such an association exists for any particular disease is to compare the number of subjects which show pial edema with those which do not show pial edema. If the ratio exceed 65.5/34.5 (the ratio of our total cases as shown above), such a relationship would be indicated.

The total number of cases of a given disease from both the edema and the no-edema column was set down and the percentages computed. For example, under the heading "Adhesive Pleurisy" I found thirty-one cases associated with pial edema and twenty cases unassociated, the proportion of one to the other expressed in percentages is 64.5 and 35.5 per cent respectively.

These figures represent the absolute percentages, since the number of cases of pial edema available for study is much larger than the number of cases without pial edema we can determine the relationship which the disease bears to the disease process in question by the use of a method which does away with the necessity of directly contrasting two unequal series. This is accomplished by reckoning percentages in each column (i. e. the pial edema, and the non-edema column) separately and then by comparing the percentages so obtained. The results in each case are found to be independent of the number of cases in either series, as they represent proportions only. Their value consists wholly in their use for purposes of comparison.

Using this method we reckon first the percentage of adhesive pleurisy (thirty-one cases) in the pial edema column (355 cases), this gives us the figure 8.7 per cent. We then similarly reckon the percentage of adhesive pleurisy (twenty cases) to the 187 cases of the "control" series which is found to be 10 per cent. These percentages being compared with one another indicate that adhesive pleurisy occurs with about the

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<sup>68</sup> The tabulated cases on which these statistics are based were so extensive that it was found impracticable to include them in this article. I shall be very glad to submit them to anyone interested.



same frequency both with and without pial edema, since the proportion of occurrence of the lesion is nearly the same in either series. If now we should find that for any given disease we had a high percentage in the pial edema column, while much lower in the no-edema column, we should infer that the lesion either played some etiological rôle or was at least definitely associated with pial edema. If on the other hand we should find the percentage in the pial edema column level with or below the percentage for the same disease in the other column we should decide that the disease bore no particular relation to pial edema.

It will be at once observed that a negative result is attained when the percentages for a given disease are the same or nearly the same in the pial edema and the control columns.

It was considered best to draw conclusions only where the figures were high enough to lend value to such percentages and for this reason lesions that appeared a few times only on the chart were not emphasized.

As a result of my preliminary studies in children and young people, it seemed wise to omit all cases under maturity from the disease columns, since it is possible that in them certain unexplained factors of development might result in confusion.

*Acute Parenchymatous Nephritis*—Reckoning the percentages by the method already explained, I found that acute parenchymatous nephritis was present in 10.9 per cent of all cases with pial edema, and in 10.6 per cent of all the cases of the series without pial edema.

*Chronic Interstitial Nephritis*—Reckoning the percentages in each column separately, chronic interstitial nephritis was found present in 32.9 per cent of all cases with pial edema and in 30.4 per cent of all cases without pial edema. The small granular kidney was present in 18.5 per cent of all subjects having pial edema and 15.5 per cent of all subjects without pial edema.

These figures do not indicate any essential relationship between pial edema and this type of kidney lesion.<sup>69</sup>

Taken altogether our figures indicated an absence of association between pial edema and acute or chronic Bright's disease.

*Syphilis*—Aside from paresis, which will be referred to again, the figures of the table did not suggest that general syphilitic infection plays a causative rôle.

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<sup>69</sup> In forty cases with pial edema the microscopical sections showed no trace of any kidney lesion, while in about the same number of cases there were noted only slight or beginning renal changes. It should be noted that the single case of uremia which we had, showed a slight degree of pial edema. There was no moisture of the cut surface apparent to suggest cerebral edema, no flattening of the convolutions or any other sign characteristic of the brains described by Traube.

*Chronic Pulmonary Tuberculosis*—This was present in 16.3 per cent of all cases of pial edema and in 26.7 per cent of all cases without pial edema

*Chronic Cardiovalvular Disease*—The figures obtained were 10.9 per cent with pial edema and 11.7 per cent without

*General Arteriosclerosis*—The figures obtained were 12.9 per cent with pial edema and 9.4 per cent without pial edema. These figures do not suggest a relationship between pial edema and arteriosclerosis

*Anemia*—We had only four cases of anemia. Two of these were associated with pial edema and two were not

*Advanced Alcoholism*—Here was found the first really significant evidence of relationship between pial edema and a disease process. Altogether there were eighty-nine cases of chronic alcoholism in the series. Of these seventy-two subjects had pial edema, or 80.9 per cent, while the remaining seventeen had dry pias, or 19.4 per cent. Reckoning the percentages for each column separately I found that chronic alcoholism was present in 20.2 per cent of all our cases with pial edema and present in only 9 per cent of all cases without pial edema. The frequency with which pial edema occurs in chronic alcoholism is thus represented by the ratio 20.2 : 9, the latter figure being taken to represent the proportion of chronic alcoholics in which no pial edema is present. It may thus be said that pial edema occurs in something like two-thirds of all cases of chronic alcoholism

*Pial Edema Associated with Transudation in Other Parts of the Body*—A. Localized or Generalized Subcutaneous Edema. My tables showed

1. Localized edema of the subcutaneous tissues occurs apparently without special relation to pial edema

2. Generalized edema. Anasarca showed a slight preponderance in the pial edema column, but the small number of cases quoted rendered this proportion of little or no value

3. Ascites. The same thing may be said of ascites as of anasarca

B. Polyserositis. I had a sufficient number of cases (forty-four) to warrant me in drawing conclusions from the percentages obtained. The percentage of serositis cases was slightly higher in the control column (20 per cent) than in the pial edema column (18 per cent). We therefore concluded that polyserositis is not associated with pial edema regularly and that it does not have necessarily the same causative factors

*Condition Associated with Acute Toxemia*—I had 466 cases which were considered as belonging in this category, 304 of these presented pial edema, the remaining 162 were not associated with this condition

Reckoning the percentages of each series as already explained, I found acute toxemia in some form present in 85 per cent of all cases that had no pial edema

*Conditions Associated with Bacteriemia*—There were 191 cases that could properly be grouped under the heading of bacteriemia, 111 of these presented pial edema, the remaining eighty had no pial effusion. I thus found bacteriemia present in 31 per cent of all our cases of pial edema, and present in 42 per cent of cases without pial edema.

*Chronic Inflammatory Lesions in the Serous Cavities*—I had altogether 104 cases that were included under this heading,<sup>70</sup> sixty-four of these showed pial edema, while forty were unassociated with pial edema.

Chronic inflammation of the serous cavities was thus present in 18 per cent of the cases of pial edema and present in 21.3 per cent of the cases without pial edema.

*Chronic Gastritis*—This condition was present in 13.2 per cent of the cases with edema of the pia and in 13.9 per cent of the cases which did not present pial edema.

*Malignant Tumors*—The figures for these cases disclose nothing of significance.

*Status Lymphaticus*—Of the fifteen cases of status lymphaticus in our series, twelve brains were large enough to completely fill the skull cavity. Pial edema was present in only three.

From the considerable proportion of large or fully developed brains noted with status lymphaticus, it might be inferred that we had here to do with a brain hypertrophy similar to that indicated by Anton<sup>71</sup> and described by Bartel<sup>72</sup> in some of his "status" cases. Such an inference should not receive undue emphasis, first, because complete weight records are not available in our series, and, second, because a large proportion of our subjects happened to be young people in whom brain volume is usually considerable.

*Insanity*—The psychopathic cases, most important because of the possibility of organic changes being present, were too few in number for comparative figures.

#### SUMMARY

*Age*—Edema of the pia was not found in my series before the fourth month. It occurred with moderate frequency from the fourth month to the fifth year. Between the fifth and sixteenth years it was absent. Beginning with the sixteenth year it rapidly increased in frequency to the period between the thirty-sixth and fortieth years,<sup>73</sup> when, following a slight sharp decline, it continued to increase though less rapidly throughout the later periods of life, becoming universal in old age.

70 Cases of serositis not included in this summary.

71 Anton, *Wahre Hypertrophie des Gehirns mit Befunden von Thymusdrüsen und Nebennieren*, Wien klin Wchnschr, 1902, LV, 132.

72 Bartel, Julius, *Ueber die hypoplastische Konstitution und ihre Bedeutung*, Wien klin Wchnschr, 1908, XLII, 783.

73 A time of life in which there is a very high death-rate among alcoholics.

*Nutrition* —Pial edema occurs independently of changes in the nutrition of the body

*Disease Conditions* —1 Pial edema does not appear to bear any particular relationship to the following common conditions chronic nephritis, chronic pulmonary tuberculosis, chronic cardiovalvular disease, acute toxemia, bacteremia, chronic inflammatory lesions in the serous cavities, and chronic gastritis

2 Pial edema is definitely associated with chronic alcoholism occurring in more than two-thirds of all cases

3 There were too few cases of syphilis, anemia and insanity to permit me to form conclusions in regard to these cases

In conclusion I wish to emphasize, first, the progressive increase of pial edema after puberty, second, the absence of any relationship between pial edema and nutritional changes in the body at large, third, the negative findings as to association between pial edema and the general disease processes studied, except alcoholism

## PART 2 THE MECHANICS AND CHEMISTRY OF THE SPINAL FLUID AND THE ANATOMY AND PHYSIOLOGY OF THE MEMBRANES

Having determined the relationship which pial edema bears to most of the important diseases, we are now in a position to study the character of the fluid present in this condition

### NORMAL DISTRIBUTION OF CEREBROSPINAL FLUID

The cerebrospinal fluid is present within the confines of the subarachnoid space, the ventricles of the brain, the perivascular spaces and the central canal of the spinal cord. It is limited externally by the arachnoid membrane (external to which, over the cortex, lies the subdural space) and internally by the pia

### DISTRIBUTION OF THE FLUID IN PIAL EDEMA

In pial edema we find that the distribution of the fluid is the same as above stated but that it is greatly increased in amount. The peculiarities as regards localization are as follows

1 It is constantly found on the superior surface of the cerebral hemispheres, especially over the vertex

2 It is found on the superior surfaces of the frontal lobes in relatively less amount

3 The anterior and posterior cisternæ are distended

4 It is found often as bleb-like accumulations on the posterior and inner margins and on the superior surfaces of the cerebellar hemispheres

5 There is occasionally a similar accumulation on the anterior poles of the temporo-sphenoidal lobes

6 There is occasionally an apparent increase of fluid in the perivascular spaces

7 There is occasionally considerable moisture of the brain tissue

8 There is occasionally increase of fluid in the subarachnoid space of the cord

9 Usually there is an increase of fluid in the lateral ventricles

10 It is rare to see any increase over the lateral regions of the cerebral cortex

No increase of fluid has ever been observed by me in the following places

A The under surface of the frontal lobes

B The under surface of the temporo-sphenoidal lobes

C The inner surface of the cerebral hemispheres

We thus observe a general tendency on the part of the excess fluid to occupy a position above that of the brain tissue proper

#### THE APPARENT SIGNIFICANCE OF THIS DISTRIBUTION

The localization of the fluid as given above is in marked contrast to that of the exudate in most cases of suppurative meningitis, especially in the epidemic type. As is well known, in most cases of meningitis the exudate is found chiefly at the base—a phenomenon that is especially noticeable in tuberculous and epidemic meningitis. The experience of this laboratory is fully in accord with the above statement and points to a tendency on the part of inflammatory changes in the meninges either to begin at the base and spread thence over the cortex, or to remain localized at the base.<sup>74</sup>

The above localization of the fluid of pial edema is in itself suggestive of the action of gravity—and it is the one which the fluid would take were there any additional room within the cranial cavity, for the reason that as the specific gravity of the brain (1.038) is greater than that of the fluid in which it lies (1.002-1.010), the brain then would naturally seek a dependent position, forcing the fluid to a higher level.

The presence of the fluid in the cisternæ pontis (and subarachnoid space) has already been mentioned.

In performing an autopsy, however, some care is necessary in order to see the fluid *in situ*, for although the arachnoid at these points is normally somewhat thicker, it is at the same time unsupported and thus is readily torn when the brain is lifted up, allowing its contents to drain away into the cranium.

When the anterior subarachnoid space is ruptured, the fluid from the posterior immediately drains across the crura cerebelli and thence into the skull cavity.

<sup>74</sup> For a consideration of this subject dealing with meningitis I would refer the reader to the recent article by W. J. Elser and F. M. Hunton, *Studies in Meningitis*, Jour. Med. Research, 1909, 11, 371.

To what degree evacuation of the lateral ventricles follows this draining through rupture of the cisternæ is difficult to say, but that it is relatively slow there is every reason to believe

The evacuation of the fluid over the cortex after removal of the brain also takes place gradually, apparently because the septa of the subarachnoid chambers offer a partial obstruction to the flow of the fluid. In some cases the arachnoid reveals an almost gelatinous mass but possibly this may be due to clotting of the fluid after removal

That the fluid over the cortex is enmeshed is shown by the following facts

- 1 The fluid over the cortex may remain *in situ* some time after the brain is removed

- 2 Puncturing the dependent areas over the cortex sometimes results in the evacuation of only a small area about the site of the puncture. To illustrate this fact we may cite the following

CASE 1879 — Pia arachnoid moderately distended with clear slightly yellowish fluid, most marked over the convexity. A small puncture (about 5 mm in diameter) was made over one of the sulci, the probe passed down through some watery and slightly gelatinous tissue to the cortex. The fluid about this puncture drained away leaving a depressed area 1 cm in diameter, but the fluid beyond this area was apparently unaffected at the end of an hour

The best way to maintain the cisternæ intact, according to my experience, has been to insert the calvarium hook beneath the occipital protuberance and tear off the calvarium from below upward, instead of from above downward (the usual practice). The dura being then cut away, the frontal lobes can be lifted up disclosing the cisternæ unruptured

The pathologist has usually considered that an excessive amount of fluid at the base and the distention of the cisternæ was an indication of an increased or high intracranial tension during life. Although it may be granted that this is the explanation for a large number of cases, we must not forget that it is not conclusive evidence. The fallacy of conclusions based on such evidence is well illustrated by the conclusion drawn by the ancient Greeks on post-mortem evidence alone that the aorta contained blood mixed with air

#### THICKENINGS OF THE ARACHNOID

In a considerable number of all pial edema cases there is a greater or less degree of opacity and thickening of the meninges. Sometimes this is chiefly limited to the area over the superior surface of the cortex along the longitudinal sinus, again it is found over cortex and cerebellum, and occasionally it has an even more generalized distribution

In every case examined by me this opacity was found to be due to connective tissue thickening of the arachnoid, involving slightly the pia-arachnoid trabeculæ, the pia itself showing no change

This lesion consists of a proliferation of the fixed connective tissue elements without exudation or vascular changes

That a process of this essentially proliferative character arising at a distance from the blood-vessels<sup>75</sup> should be the cause of the large fluid accumulations seems hardly possible

#### CHEMISTRY OF FLUID IN PIAL EDEMA

The final determination as to the inflammatory or non-inflammatory character of the fluid rests in the last analysis with the chemical examination. It is a well-known fact that fluid collected after death is worthless for examination, since post-mortem changes render chemical tests of doubtful value.<sup>76</sup> The most satisfactory method is to collect the fluids *intra vitam* and to verify the findings thus obtained at autopsies. Such procedure, naturally, is attended with many disappointments.

With the exception of one case reported by Dufour,<sup>77</sup> I have so far been unable to find in the literature any satisfactory record of analyses of spinal fluid from subjects of "wet-brain." A specific test for serum albumin or globulin rather than for protein should be of value in determining the question of possible inflammatory influences. Serum albumin is not a normal constituent of cerebrospinal fluid<sup>78</sup> and therefore its presence in the class of cases under discussion should indicate an exudative or transudative process. The absence of traces of serum albumin, in the light of our present knowledge of the secretory origin of the cerebrospinal fluid, would therefore indicate that the spinal fluid is the product of normal secretion. Professor Hastings has kindly supplied me with a series of analyses on this class of cases, and these will now be considered.<sup>79</sup>

A spinal fluid from a subject of alcoholic "wet-brain" examined by him showed a protein content of 0.005 per cent, a minimum normal figure.

The figure for protein quoted above speaks strongly against the presence of either transudate or exudate in the spinal fluid of these cases. Professor Hastings analyzed several other specimens of alcoholic "wet-brain" without reference to the protein content.

<sup>75</sup> The blood-vessels lie close to the pia.

<sup>76</sup> Myers V. C. *The Cerebrospinal Fluid in Certain Forms of Insanity with Special Reference to the Content of Potassium*, Jour. Biol. Chem., 1909, vi, 115.

<sup>77</sup> Dufour H. *Cytologie du liquide céphalo rachidien dans un cas de ménin-gite chronique alcoolique*, Bull. et mém. Soc. méd. d'hôp. de Paris, 1901, xiii, 1035.

<sup>78</sup> Halliburton in Kruke's *Physiology*, Ed. 1908, p. 178.

<sup>79</sup> Spinal Fluid Analyses in Alcoholic Wet Brain Cases, loaned by Professor Hastings of Cornell University.

The amounts in these cases ranged from 25 to 88 c c , all specimens were clear, sterile and free from coagulum or sediment. The cytological count was as given in Table 1.

TABLE 1—CELL-COUNT—100 FIELDS

Case	Polys	Small Monos	Endothelial Cells	N B Cs
1	0	2	0	12
2	0	7	1	18
3	0	6	0	27
4	0	1	2	1,156 *
5	0	1	0	0
6	0	3	0	0
7	0	1	0	1
8	0	0	0	0

\* First tube contaminated with blood

The conclusions from these analyses were that the fluid of alcoholic "wet-brain" did not differ from normal cerebrospinal fluid.

#### CIRCULATORY CHANGES IN THE MEMBRANES WITH PIAL EDEMA

It is well known that it is difficult to determine from post-mortem findings the circulatory conditions which were present during life in cases of pial edema, since alterations in the vascular system of the brain occur frequently just prior to and at the time of death.

My findings in regard to the condition of the meningeal circulation in pial edema (from post-mortem study of 100 cases) are as follows:

	No of Cases
1 Active congestion of membranes, brain normal	12
2 Passive congestion of membranes, brain normal	21
3 Active and passive congestion of membranes, occurring together, brain normal	12
4 Active congestion of membranes with anemia of brain	1
5 Passive congestion of membranes, with anemia of brain	1
6 Active congestion of membranes and brain	5
7 Passive congestion of membranes and brain	7
8 Active and passive congestion of membranes and brain	10
9 Membranes and brain normal	20
10 Pia arachnoid normal, brain anemic	4
11 Pia arachnoid normal, brain congested	1
12 Anemia of brain and membranes	6

The commonest condition found was thus passive congestion of the membranes (present in 21 per cent). The next most common was an apparently normal condition of the vessels of the brain and meninges (20 per cent). Active congestion of the membranes and a condition of active and passive congestion of the membranes, occurred in 12 per cent. Anemia of the membranes and brain was present in 6 per cent. Altogether passive congestion of the membranes (either alone or combined) occurred in fifty-one cases (51 per cent), whereas active congestion was



present in only forty cases (40 per cent) The preponderance of passive congestions in this series agrees with the statement of Kaufmann<sup>80</sup> that most of the cerebral congestions observed at autopsy are of the passive type

The frequent occurrence of passive congestion can hardly be taken as an indication that passive congestion has any special influence in the production of pial edema because there is nothing to show that it is more common with pial edema than with the general run of autopsy cases Furthermore, the wide variety of other vascular conditions cited in this series shows that pial edema bears no constant relation to any particular circulatory condition as seen at autopsy

### PART 3 THE PHYSICS AND MECHANICS OF PIAL EDEMA

My observations thus far have been with a view to determine under what conditions pial edema is found Let us now consider from a more theoretical standpoint the mechanics involved in the causation of accumulations of fluid in the pia-arachnoid Two hypotheses present themselves

1 The accumulation of fluid is the result of an increase of secretory activity of the choroid plexus, or a lack of resorption, leading to a compression of the brain substance, or

2 The fluid has simply collected as a result of some undetermined process leading to a reduction in size of the brain

The first hypothesis to be discussed is whether the fluid can actually compress the brain so as to give rise to the appearances met with in pial edema

Before doing so, however, we must review certain well-established mechanical principles, a correct understanding of which is essential to a comprehension of some of the more complex problems in connection with pial or cerebral edema and serious meningitis

It will not be necessary to sketch the outlines of the study of intracranial mechanics since the time of the second Monroe<sup>81</sup> Let me present only the points that are involved and endeavor briefly to show their bearing on our subject

Of fundamental importance is the old question "Is the craniospinal canal independent of the influence of atmospheric pressure?"

Certain early writers, as Monroe, Kellicott,<sup>82</sup> Abercrombie and Reid,<sup>83</sup> and nearly all modern writers, among whom may be included Naunyn

80 Kaufmann, Eduard *Lehrbuch der speziellen pathologischen Anatomie*, Berlin, 1904, p 983

81 Monroe, Alexander *Observations on the Structure and Functions of the Nervous System*, Edinburgh 1783

82 Kellicott George *Reflections on the Pathology of the Brain* *Tr Med Chir Soc Edinburgh*, 1824, 1, 84

83 Reid *Physiol, Anat and Path Researches* 111

and Schrieber,<sup>84</sup> Falkenheim and Naunyn,<sup>85</sup> Horsley and Spencer,<sup>86</sup> Horsley,<sup>87</sup> Spencer,<sup>88</sup> Roy and Sherrington,<sup>89</sup> Hill,<sup>90</sup> Kocher,<sup>91</sup> Cushing<sup>92</sup> and many others, have decided that it is

The earlier negative conclusions of Burrows<sup>93</sup> and Donders<sup>94</sup> were seriously considered for over half a century after their promulgation<sup>95</sup>

Leonard Hill's argument in favor of the absence of atmospheric pressure within the skull cavity was as follows

If the spinal cord of a dog be divided or the splanchnic nerves be cut and the animal be placed in the vertical feet down position the blood pressure in the brain will under the influence of gravity, fall to zero. If the skull be now trephined, and the dura be rapidly opened, the brain, which was before in close apposition with the dura, may now be seen collapsing under one's very eyes, as it is emptied of blood by atmospheric pressure<sup>96</sup>

Additional evidence in confirmation of Leonard Hill's view that atmospheric pressure was absent in the skull cavity was obtained by the following experiments

EXPERIMENT 1.—A trocar was introduced into the spinal canal of a prone intact cadaver and a small amount of fluid ran out owing to persistence of the pressure existing during life. No more escaping, suction was applied by means of a syringe and a little more fluid was obtained (altogether about 3 cc). The trocar was then removed and the calvarium opened. The cisternæ contained the usual amount of fluid and likewise the spinal canal

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84 Naunyn, B., and Schrieber, J. Ueber Gehirndruck, *Arch f exper Path u Pharmacol*, 1881, *xiv*, 1

85 Falkenheim, H. and Naunyn, B. Ueber Hirndruck, *Arch f exper Path u Pharmacol*, 1887, *xiii*, 261

86 Horsley, V., and Spencer, W. *Phil Tr*, 1891

87 Horsley, Sir Victor. The Mode of Death in Cerebral Compression and Its Prevention, *Quart Med Jour* London, 1894, *ii*, 305, The Structure and Functions of the Brain and Spinal Cord, P. Blakiston's Son & Co., Phila., 1892

88 Spencer, W. The Central Nervous Mechanism of the Respiration, *Airs and Gale Lectures*, *Lancet*, London, 1895, *xxxv*, 532

89 Roy, C. S., and Sherrington, C. S. On the Regulation of the Blood Supply of the Brain, *Jour Physiol*, 1890, *xi*, 85

90 Hill, Leonard. The Physiology and Pathology of the Cerebral Circulation, London, 1896, Churchill

91 Kocher, T. Hirnerschutterung, etc. *Specielle Pathologie und Therapie in Nothnagel*, Wien, 1901, Ed 2, Part, 3, 18

92 Cushing, H. Some Experimental Clinical Observations Concerning States of Increased Intracranial Tension (Mutter Lecture) *Am Jour Med Sc*, 1902, *cxxiv*, 375, The Blood Pressure Reaction of Acute Cerebral Compression, etc., *Am Jour Med Sc*, 1903, *cxxv*, 1017, A Discussion of Some Remote Effects of Cerebral Injuries, etc., *New York Med Jour*, 1907, *lxxxv*, 97, 61, 208

93 Burrows, George. Disorders of the Cerebral Circulation and on the Connection Between Affections of the Brain and Diseases of the Heart, Philadelphia, 1848, Lea and Blanchard

94 Donders, F. C. *Nederl Lancet*, 1850

95 Reynolds and Bastian. Congestion of the Brain in Reynolds' System of Medicine, 1879

96 Hill, Leonard. The Physiology and Pathology of Cerebral Circulation, p 36

EXPERIMENT 2—Calvarium removed first Cisternæ intact and seen to be full of clear fluid Spinal puncture, 12 cc fluid came through cannula as if under slight pressure Cisternæ re examined and found full as before Brain covered with wet cloths, in ten minutes fluid at the base had all disappeared into the cord

The first experiment shows that outside air-pressure does not influence the contents of the craniospinal canal, since it was impossible to evacuate the fluid (except that in excess, and a slight amount in addition, due, possibly, to the stretching inward of the spinal membranes) through the single opening

When, however, as in Experiment 2, a second opening was made and outside air-pressure admitted, there was no obstacle to the ready evacuation of the fluid in the direction of gravity

The principle involved in these experiments is very easy to demonstrate with suitable apparatus It will be observed that the fluid in the craniospinal canal in the first case has behaved as might be expected were atmospheric pressure absent

There are certain anatomical features that require consideration in this connection

Figure 2 represents the craniospinal canal, to all intents and purposes a closed cavity, the heavy black line its bony confines, the thinner line within represents the arachnoid which determines the outer limit of spinal fluid While this membrane is not actually adherent to the overlying dura and bony walls, it lies in close apposition within the skull and is therefore incapable of any distention outward In the spinal canal, however, it (together with the dura) lies like a sac at some distance from the bony walls, being separated from these walls by loose and compressible areolar tissue containing a plexus of veins<sup>97</sup>

Any increase of fluid within such a cavity must find room through distention of the sac outward<sup>98</sup>

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97 Schafer, E A In Quain's Anatomy, Spinal Cord and Brain, Part 1, p 3, Longmans, Green and Co, London, 1893

98 The suggestion that the theca vertebralis plays a part during life in the accommodation of excessive amounts of spinal fluid and the production of high intracranial pressure will doubtless arouse opposition among those who have demonstrated vascular relationship to pressure phenomena I do not, however, disagree with Dr Ferrier's statement that under normal conditions the ebb and flow between the cranial and spinal cavities is so small as to be practically a negligible quantity, but I desire to point out that no experimental work so far done is of much value in helping us to reach conclusions in the present work largely because of the fact that none of these experiments has been arranged so as to show what mechanical changes take place when resorption of spinal fluid is prevented and when the high pressure is caused by an excessive amount of the fluid itself My suggestion that distention of the theca is a factor is based on a study of the behavior of fluids within the craniospinal canals of cadavers The distensibility of the sac under these circumstances has long ago been demonstrated but Dern (Jour Path and Bacteriol, 1893, 1, 28) and others have been inclined to doubt whether such a process could take place in living subjects

It is of course unlikely that such a process would take place unless there were some hindrance to resorption

It will be readily seen that while fluid can, at the outset, be forced into this sac without greatly raising intracranial pressure, after an amount has been forced in sufficient to crowd the tissue of the surrounding space and stretch the membranes considerably, there will be an ever-increasing resistance for each cubic centimeter forced in, until finally a point is reached at which no more fluid can be introduced, owing to the surrounding tissues having reached their limit of compressibility. It is the elastic recoil of these membranes which are put on the stretch and the adjacent tissues which are compressed that, to a certain extent, gives the measure of intracranial tension, and thus when a cannula is introduced into this distended sac the tension of the tissues and membranes causes the expulsion of excess of all fluid, until the pressure is relieved.

Not all of the fluid, however, drains away, for a certain amount is necessary to fill various areas in and about the brain substance and the spinal cord. In the skull cavity the amount of this fluid scarcely varies

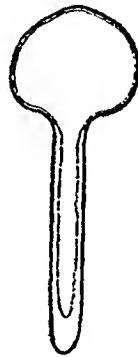


Fig. 2—Diagram of craniospinal canal, heavy black line, bony confines, thinner line within, the arachnoid which determines the outer limit of spinal fluid.

since it cannot increase against the bony walls, nor can it diminish in amount anywhere without producing a vacuum at that point.

In the canal, on the other hand, the sac will retain only sufficient fluid to maintain equilibrium, that is to say, although a slight excess positive pressure is normally maintained, enough fluid will run out of a cannula to reduce this slight positive pressure to zero. Zero does not mean absence of fluid, but merely that the pressure within the spinal canal has dropped to the normal air-pressure.

Having considered the relation of atmospheric pressure to the skull cavity, and obtained some idea as to the relationship which exists between the membranes and the phenomena of intracranial tension, we may now go a step further and attempt to determine the effect of the factors just discussed on the brain itself. The difficulties involved in a study of this phase of our problem are all the greater when we realize that we know very little about two essential factors, *i. e.*, first, the density or compres-

sibility of brain tissue and second, the permeability of the brain to fluids under pressure

Our task now is to determine whether, according to the laws of physics and hydraulics, it would be possible for the brain (its blood-vessels excepted) to suffer compression through general increase of intracranial pressure

The subject of compressibility must first be considered. Compression, broadly speaking, is brought about through expression of content. It is true that molecules are very slightly compressible, but, as indicated below,<sup>99</sup> reduction in size from molecular compression would be so insignificant as to deserve but little attention.

For example, take a dry sponge, it is readily compressed in the hand through expulsion of the air molecules from its chambers. On being allowed to soak up water it gains in size and weight but still remains compressible through the ready loss of the water under pressure. If the same saturated sponge be now placed in an air-tight rubber bag which fits snugly at all points, compression is no longer possible, since there is now no longer any means of escape for its fluid contents.

The same principle applies to all homogeneous semifluid bodies, compression takes place by expression of air or fluid content where possible but when air or fluid cannot be expressed the body is termed incompressible.

Since, then, compression sufficient to be visible can only take place through expression of content, it is only fair to inquire whether such compression could occur within the skull cavity. An attempt to force fluid into a receptacle already filled with a solid or fluid would not result in an increase in the amount within the receptacle, but its molecules would simply transmit the added pressure to the walls and there is no reason to assume that the brain is to be looked on as an exception to this physical principle. Compression cannot take place without corresponding allowance being made for the displaced substance in the enclosing medium. Lacking this allowance any reduction of size is impossible.

A converse process, i. e., brain swelling, requires a corresponding displacement of content that is under ordinary circumstances allowed for by the evacuation of spinal fluid—a process that takes place when tension is somewhat raised.

While there is, according to the above explanation, no ground for the belief that general high intracranial pressure could bring about visible changes in the size or contour of the brain it is barely possible that pressure may be a factor in inducing molecular compression, for although such molecular compression as might result from those degrees of intra-

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<sup>99</sup> Water, which is relatively incompressible has increased in weight only about 0.03 pound to the cubic foot at a depth of 350 feet. *Treatise on Hydraulics*, Merriam, 1906 p. 11.

cranial pressure that have been registered clinically are very slight when judged from the standpoint of the physicist, still so sensitive a tissue as the nerve cell is known to be, might appreciate the very small increases of molecular densities brought about in this manner.

We are not, however, justified in speculating on the chances of molecular compression within the brain until more is known about the compressibility of gray matter, if, for instance, this is slight, pressure would be transmitted through the brain to the surrounding bony confines, the intervening cells of the gray matter being but little affected. On the other hand, were the compressibility greater, pressure would not be so readily transmitted and a slight amount of molecular compression would doubtless result.

The influence of pressure from general causes has already been pointed out, we may now briefly contrast with these the effects of pressure due to local conditions, namely, those caused by hemorrhage or due to tumor growth.

The multiplication of tumor cells exerts, as in other organs, its first effect locally—namely, in compression and pressure-atrophy of the adjacent tissues and in compression of the adjacent vascular structures in the brain. Further compensation for any increase in growth or hemorrhage develops at the expense of the spinal fluid, which is resorbed, while when intracranial tension exceeds that in the venous structures the latter become somewhat compressed.<sup>100</sup>

Striking post-mortem evidence of compression through any intracranial growth is seen in the marked flattening of one or both hemispheres, the dry pia and the marked diminution in amount of blood found in the pial vessels.

For these reasons I believe that compression of the brain by the fluid in cases showing pial edema is an impossibility, and that the appearances observed in cases of pial edema are not attributable to the pressure of the fluid. These appearances are thus the result of some other agency, in all probability they represent a redistribution or replacement process.

#### PART 4—PHYSICS AND MECHANICS OF PIAL EDEMA

For the purpose of determining whether or not I had to deal with a replacement process, I began the rather elaborate system of post-mortem observations which are now to be described.

The cases on which these observations were made were taken from the general autopsy service of Bellevue Hospital. The technic was as follows:

<sup>100</sup> The subject of the effects of pressure on the vascular structures within the skull has received so much attention of late that elaboration in this paper would seem superfluous. The following contributions are especially important: Ferrier, David. *The Harveyian Oration on the Heart and Nervous System*, Lancet, London, 1902, 11, 1099; Cushing, H. *ibid*.

## TECHNIC

When possible the calvarium was removed before the thorax was opened in order to prevent a redistribution of the blood. Many times, however, it was impracticable to halt the general autopsy work for this rather considerable interval and the result was that when the thorax was opened and the large veins were cut, as soon as the calvarium was opened and the relative negative pressure within the skull cavity removed, a considerable amount of blood would drain into the thorax from the vessels of the head.

The chief effect of this loss of blood was a reduction in the volume of the brain, causing a discrepancy between the volume of the cranial cavity as afterward registered and the total measured cranial content. The influence of this factor on the weight, specific gravity and volume of the brain, however, need not be considered, as when the blood was not evacuated into the thorax, it would be lost as the brain was being removed, and thus would not enter into subsequent computations.

As soon as the calvarium was removed, a pan was placed beneath to catch the drippings, and the tentorium carefully cut away and laid aside. The hemispheres were gently pushed apart along the great longitudinal furrow, and a small incision made through the corpus callosum into each lateral ventricle, the contents of which were withdrawn by a pipette and measured.

The brain was then removed and allowed to drip into a pan until the watery fluid over the cortex and elsewhere, had quite disappeared. It was then weighed in the air and its weight recorded. Following this it was weighed in water at 15 C with the same balance and its specific gravity computed.

It is important to note here that considerable variation in specific gravity was unavoidable owing to the fact that in many of the brains it was impossible to get rid of all the spinal fluid which was retained in pockets and corners of the sulci. This increased the weight in air, but not in water, and as a very few grams weight will make quite a wide variation in specific gravity, it will be seen that I was here often confronted with an important source of error.

The brain proper having been disposed of, the drippings, the free fluid in the calvarium, and the ventricular fluid, were carefully collected and measured.

The portions of dura cut away were measured in water giving the number of cubic centimeters displaced, and, finally, the capacity of the skull cavity was measured by means of dried peas.

By the addition of the total fluid content of the calvarium with the dura and the brain volume (in cc), a fairly accurate estimate of the total cranial content is arrived at. Comparing this figure with that representing the cranial volume a very slight error is observed in those cases in which the cerebral blood was allowed to escape into the thorax previous to the examination of the head. In the latter cases the discrepancy represents this loss and can be readily identified by a study of the chart.

Having ascertained the above data, it was thought to be best for purpose of study to arrange the cases in groups corresponding to the amount of pial edema present.

On examining Table 2, in reference to the specific gravities, the recognized tendency for brains to become lighter at the extremes of age is observed.

There is, however, a most important point which these tables have clearly brought out, i. e., that there is a gradually increasing discrepancy between the capacity of the brain cavity and the volume of the brain, which is directly proportional to the degree of pial edema present.

In Group 1, cases without pial edema we see that the average discrepancy is only about 29 cc, this figure being presumably the equivalent





Age (yr)	Sex	Anatomical Diagnosis	Amount of Fluid in Ventricles (cc)	Specific Gravity of Cerebrospinal Fluid	Weight of Brain (gm)	Specific Gravity of Brain	Volume of Brain (cc)	Volume (cc) of Excised Dura (Tensorium and Falx)	Total Fluid in Cranium (cc)	Total Capacity of Cranium (cc)	Discrepancy Between Membrane and Capacity of Skull (cc)
1,964	50	Cardiomephalic	6 Clear	1.007	1401	1.030	1359	29	63	1560	72
2,057	37	Brain tumor	8 Contam		1230	1.038	1184	22	53	1270	64
2,082	33	General miliary tuberculosis	12 Clear	1.007	1271	1.035	1227	50	106	1385	108
2,101	?	Chronic pulmonary tuberculosis	5 Clear	1.003	1041	1.040	1003	21	76	1100	76
2,106	21	Chronic tuberculous peritonitis	5 Clear	1.006	1115	1.038	1074	20	58	1225	131
2,113	40	Chronic alcoholism, ginglymus cervicis	8 Clear	1.005	1268	1.038	1221	32	90	1380	127
Average age, 36.2 years			Average specific gravity of brains, 1.0365		Average discrepancy, 96.3 cc						
Group 4—Cases with Marked Edema											
1,964	54	Carcinoma of esophagus, bronchopneumonia	4	1.009	1347	1.037	1299	35	67	1510	176
2,049	56	Acute general miliary tb, tb of meninges	18	Contam	1447	1.033	1400	29	100	1635	206
2,085	1	Marasmus, congenital diplegia			668	1.020	646	10	Collected 100, remainder lost	830	162
2,108	40	Chronic pulmonary tuberculosis	3	1.007	1194	1.038	1149	22	115	1340	169
2,131	67	General arteriosclerosis	24 Clear	1.007	1197	1.039	1151	30	125	1345	164
2,147	70	Chronic miliary pulmonary tuberculosis	18		1375	1.038	1286	40	138	1550	224
Average age (children excluded), 57.6 years			Average specific gravity of brains, 1.0258		Average discrepancy, 183.5 cc						
Group 5—Cases with Exuberant Edema											
2,052	66	Chronic interstitial nephritis	7 Clear	Contam	1000	1.027	974	27	122	1190	189
2,115	61	Chronic tuberculous bronchopneumonia	25 Clear		1231	1.041	1182	20	175	1430	228
Average age, 63.5 years			Average specific gravity of brains, 1.034		Average discrepancy, 208.5 cc						

of the cerebrospinal fluid present. In these cases the brain may be assumed to fill the skull cavity within physiological limits.

In Group 2, where the edema is slight, there is an average total discrepancy of 53 cc, an increase of 24 cc over the preceding class.

As the edema increases, there is a corresponding increase in the discrepancy. In the remaining groups it is, with moderate edema, 96 cc, with marked edema, 183 cc, and lastly, in the two cases of excessive edema in the series the discrepancy culminates with 208 cc as a maximum, this in spite of the fact that one of the cases examined had a very small skull. This discrepancy can, of course, be interpreted in only one way, i. e., that the brain has become so reduced in size as not to fill completely the cranial vault.

Were compression the cause of this reduction in size there should be a corresponding increase in the specific gravity of these brains, proportional to the degree of edema. This, we see, is not present, indeed, if it is permissible to say anything at all in this connection, it is that the specific gravity has fallen slightly with the higher grades of edema. To say merely that the condition is a hydrocephalus *ex vacuo* does not, by any means, dispose of the whole subject, let us therefore resume the consideration of the data before us.

Leaving out of account the two cases cited, in very young children, we observe that the more vigorous periods of life coincide with the milder degrees of discrepancy between brain and skull cavity, while the more marked differences are exhibited in the more advanced periods of life. It has been universally recognized that shrinkage of the brain is an accompaniment of extreme old age, but the extent to which this phenomenon reaches back into the years of vigorous manhood has not been generally considered.

Table 3 shows the brain weight at different ages, for children only, by Parrot,<sup>101</sup> Pfister,<sup>102</sup> and Marchand,<sup>103</sup> through childhood up to the twenty-fifth year by Vierordt,<sup>104</sup> at all ages Boyd,<sup>105</sup> Meynert<sup>106</sup> and Handmann,<sup>107</sup> and from the twentieth to the ninety-fifth year, Bischoff.<sup>108</sup>

101 Parrot. Bull. Soc. d'Anthropol. de Paris, 1887, le Mars.

102 Pfister, H. Ueber das Gewicht des Gehirns und einzelner Hirnthelle beim Saugling und alteren Kinde. Neurol. Centralbl., 1903, xxi, 562.

103 Marchand. Ueber das Hirngewicht des Menschen, Abhandl. d. math.-phys. Classe d. kgl. Sachs. Gesellsch. d. Wissensch., 1892, xvi, 437.

104 Vierordt, H. Anat. Physiol. u. Physikal. Daten und Tabellen, 1906, Jena.

105 Boyd. Phil. Tr. Roy. Soc. London, 1861, ch. 242.

106 Meynert, Th. Das Gesamtgewicht und die Theilgewichte des Gehirnes in ihren Beziehungen zum Geschlechte, dem Lebensalter und dem Irrsinn, untersucht nach einer neuen Wägungsmethode an den Gehirnen der in der Wiener Irrenanstalt im Jahre 1866 Verstorbenen, Vrtljschr. f. Psychiat., 1867, ii, 125.

107 Handmann, Ernst. Ueber das Hirngewicht des Menschen, etc., Arch. f. Anat. u. Entwicklungsgesch., 1906, p. 1.

108 Von Bischoff, T. L. W. Das Hirngewicht des Menschen (von P. Neusser). Bonn, 1880.

TABLE 3—GROUP 1—BRAIN WEIGHTS OF CHILDREN AND YOUNG ADULTS\*

VIERORDT			PARROT			PFISTER			MARCHANT		
Age	Weight (gm )		Age	Weight (gm )		Age	Weight (gm )		Age	Weight (gm )	
	Males	Females		Males	Females		Males	Females		Males	Females
Newborn	381	384					340*	330*		371	361
1 month	463	402		364	331	2-4 wks	431	396		411	375
2-3 mos	548	527		490	412	2 mos	461	415		474	450
4-6 mos	632	575		575	552	3 mos	519	504		612	587
7-9 mos	733	771	7-11 mos	778	719	4-5 mos	583	562			
10-11 mos		693				6-8 mos	733	666	7-11 mos	796	802
1 year	944	872				9-10 mos	786	684			
2 years	1,025	960	1-2 years	964	913	11-12 mos	851	727		967	893
3 years	1,112	1,040					958	901	1-2 years	1,011	896
4 years	1,327	1,138	2-4 years	1,167	1,063		1,099	1,044	2-3 years	1,080	1,099
5 years	1,282	1,220					1,183	1,091	3-4 years	1,310	1,024
6 years	1,353	1,258	4-6 years	1,261	1,137				4-5 years	1,273	1,183
7 years	1,348	1,295							5-6 years	1,343	1,245
8 years	1,366	1,150				5-8 years	1,219			(at 5 yrs)	
9 years	1,425	1,242							6-9 years	1,360	1,242
10 years	1,417	1,267							10-14 yrs	1,346	1,221
11 years	1,379	1,238				9-12 yrs	1,285	1,265			
12 years	1,415	1,245					1,289				
13 years	1,475	1,255									
14 years	1,289	1,345									
15 years	1,471	1,235									
16 years	1,435	1,272									
17 years	1,409	1,236							15-19 yrs	1,404	1,309
18 years	1,441	1,324									
19 years	1,384	1,234									
20 years	1,444	1,228									
21 years	1,425	1,319									
22 years	1,348	1,280									
23 years	1,402	1,277									
24 years	1,419	1,248									
25 years	1,428	1,230									

\* Parrot's, Pfister's and Marchand's ages same as in Vierordt's column unless otherwise indicated

## GROUP 2—BRAIN WEIGHTS AT ALL AGES\*

HANDMANN			MEYNERT			BOYD			BISCHOFF		
Age	Weight (gm )		Age	Weight (gm )		Age	Weight (gm )		Age	Weight (gm )	
	Males	Females		Males	Females		Males	Females		Males	Females
	239†	247†				Newborn	393	347			
7 days	404†	377									
8-30 days	357	357				1-3 mos	493	495			
2-3 mos	485	486					603	560			
4-6 mos	650	490				7-11 mos	777	709			
7-12 mos	830	817				1-2 years	941	845			
2 years	1,075	998				2-4 years	1,097	997			
3 years	1,208	1,088				4-6 years	1,140	1,137			
4 years	1,185	1,173	1-19 yrs	1,114		6-14 yrs	1,304	1,156			
5 years	1,245	1,225				15-19 yrs	1,376	1,246			
6 years	1,215									1,396	1,234
7-9 years	1,345	1,283				20-30 yrs	1,358	1,239		1,365	1,233
10-14 yrs	1,400	1,215				30-40 yrs	1,366	1,222		1,366	1,240
15-17 yrs	1,429	1,281				40-50 yrs	1,348	1,214			
18-19 yrs	1,328	1,226				At 50 yrs	1,352	1,208			
20-29 yrs	1,392	1,252		1,306	1,169	50-60 yrs	1,345	1,225		1,375	1,200
30-39 yrs	1,367	1,246		1,326	1,167	60-70 yrs	1,315	1,210		1,323	1,175
40-49 yrs	1,358	1,247		1,317	1,173	71-80 yrs	1,290	1,170		1,279	1,121
						Over 80	1,284	1,137	80-85 yrs	1,023	942
50-59 yrs	1,357	1,227		1,240	1,174						
60-69 yrs	1,326	1,208		1,289	1,161						
70-79 yrs	1,282	1,175		1,206	1,098						
80-84 yrs	1,250	1,126	80-89 yrs		1,148						

\* Meynert's age grouping follows Handmann's and Bischoff's, is similar to Boyd's except when otherwise indicated

† Boys under 49 cm length of body  
 ‡ Boys over 50 cm length of body

\* Girls under 50 cm length of body  
 || Girls from 50 to 55 cm length of body

The highest figures reached in Vierordt's column, Table 3 (1,475 gm) occur at the age of 13 years in males. Among the females the highest weight recorded is (1,345 gm) at the age of 14. This table, however, can scarcely be considered complete enough for our purposes.

Boyd's figures give the period of maximum weight as between 15 and 19 years, with a subsequent loss up to the age of 80 of about 90 gm.

Bischoff represents an irregular decline from 20 to 30 onward in males. His highest figure quoted in females, however, is between 40 and 50.

Handmann finds that the greatest brain weight occurs in males between the seventh and fifteenth years and that after the twentieth year there is a gradual and steady decline. In females, curiously enough, his highest recorded brain weight (1,283 gm) occurs in rather young children, seventh to ninth years. There is a slightly lower figure given for the period between the fifteenth and seventeenth years. There is, however, no rapid decline evident until middle age.

Peacock gives the maximum weight as between 25 and 30, Broca<sup>109</sup> at between 30 and 35, while Meynert's figures indicate that loss of weight begins even later in life.

Blakeman<sup>110</sup> concluded that the human prime in brain weight seems to fall before the twentieth year and that after this period there is on the whole a continuous fall. Taken altogether these data afford clear evidence that recessive changes within the brain begin often quite early in life, although it is evident from the study of even such limited data as I present that in some cases the brain maintains its maximum volume until its possessor is well advanced in years.

From these data there may be noted a strong tendency on the part of the age curve of pial edema as plotted out from my series of 375 cases to coincide with a curve plotted out in accordance with a scale of loss of brain weight for equivalent ages, that is to say, as the curve for pial edema rises, the average of brain weights will be found to fall correspondingly from point to point on the chart.

Apart from the sudden rise in the pial edema curve between 30 and 40 years, due to the inclusion of the large number of alcoholics dying within this period, the evidence is strong that pial edema coincides with the reduction of brain weight that is common after puberty, and, such being the case, I infer that it is secondary to a reduction in size of the brain and that it therefore represents a replacement process due to the brain shrinkage.

<sup>109</sup> Quoted from Quain's Anatomy, III, Part 1, p. 178.

<sup>110</sup> Blakeman, J. A Study of the Biometric Constants of English Brain Weights and Their Relationships to External Physical Measurements, Biometrika, 1905, IV, 124.

Such a shrinkage is of course to be looked on as entirely physiological. The discrepancy between the skull and the brain is doubtless to a certain extent modified by the sensible shrinkage of the head diameters described by Blakeman<sup>111</sup> as occurring in general hospital cases, but this is really slight, being very roughly only about 5 mm between the twentieth year and old age.

Pathological shrinkage of the brain, that due to contraction caused by disease, has long been recognized. Clapham<sup>112</sup> in 1873, Crichton-Browne,<sup>113</sup> 1879, and Mercier<sup>114</sup> in 1891 published observations on the subject of lessened brain weights in the insane drawn from large series of cases. Boyd's figures, with which Crichton-Browne agrees, are so tabulated as to be readily intelligible, they are given in Table 4.

Donaldson in considering this table<sup>115</sup> regards the last three on the list as those in which wasting of the brain takes place.

TABLE 4—BRAIN WEIGHT IN THE INSANE AS GIVEN BY BOYD\*

MALES			FEMALES		
Diagnosis	No of Cases	Encephalic Wt, gm	Diagnosis	No of Cases	Encephalic Wt, gm
Mania	108	1,393	Mania	107	1,227
Recurrent mania	30	1,383	Recurrent mania	33	1,238
Melancholia	52	1,335	Melancholia	68	1,261
Epilepsy	89	1,310	Epilepsy	60	1,216
Dementia	49	1,307	Dementia	61	1,188
General paralysis	122	1,304	General paralysis	30	1,162
Senile dementia	29	1,259	Senile dementia	12	1,226

\* Crichton-Browne, *Brain*, 1879, i, 511, quoted from H. H. Donaldson's *Growth of the Brain*.

Kaufmann<sup>116</sup> describes general cerebral atrophy in connection with old age, prolonged illness, chronic lead poisoning, alcoholism and dementia paralytica. Our researches in connection with pial edema confirm the statements in regard to old age and alcoholism and indirectly disagree with that in regard to prolonged illness,<sup>117</sup> but do not cover the other conditions mentioned.

Altogether I may summarize by saying that pial edema follows atrophy of the brain, first, in the great majority of instances as a result of

111 Blakeman, J. *Biometrika*, 1905, iv, 138. He found no shrinkage in the head diameters of criminals, but states that the subject has not been fully worked out for the general population.

112 Clapham, C. *The Weight of the Brain in the Insane*, West Riding Asyl. Med. Rep., iii, vi.

113 Crichton-Browne, J. *The Weight of the Brain and Its Component Parts in the Insane*, *Brain*, 1879, i, 504, ii, 42.

114 Mercier, C. A. *The Weight of the Brain in the Insane with Reference to Hemispheres, Lobes, Brain Stem and Cerebellum*, *Jour. Ment. Sc.*, 1891, xxxiii, 207.

115 Donaldson, H. H. *Growth of the Brain*, 1895, pp. 137-140.

116 Kaufmann, E. *Spezielle Pathologische Anatomie*, Ed. 5, Berlin, 1909, p. 1094.

117 My figures already given under "Nutrition" in Part I have shown an absence of relationship between pial edema and wasting of the rest of the body.

physiological changes beginning at or soon after puberty, second, in a smaller group as the result of certain pathological conditions, notable among which are chronic alcoholism<sup>118</sup> and certain forms of insanity

My earlier review and demonstration of the principles underlying intracranial pressure is justified, first, by the necessity of ruling out a hypothetical cause (namely, local compression) for the appearances noted in cases of well-marked subarachnoidal edema, secondly, by the evident need of restating these principles to those observers on serious meningitis who have apparently overlooked them, and, lastly, by the necessity of reviewing the fundamentals before entering into such discussion of the more complex and minute phases of the question as is inevitable in a consideration of the relations that exist between the present work and the conceptions of the Traube school, the observations of Kolisko and the experimental work of Mott and of Cannon

In connection with Mott's work, his findings of increased fluid in the skulls of general paralytics<sup>119</sup> are in accord with the well-recognized tendency of these cases to brain shrinkage and consequent hydrocephalus *ex vacuo*, as already pointed out. It must not be forgotten that brain shrinkage usually implies a widening of the perivascular spaces similar to that seen in senile brains and graphically described by Gowers<sup>120</sup>. Such a condition is frequently encountered at autopsy, and it is not strange that the excessive moisture found on section of the brain should often be erroneously ascribed to a dilatation of those spaces by serum transuded from the blood-vessels. As a matter of fact it seems to be questionable whether dilatation of these "lymphatic" spaces is a possibility. Mott adheres to the view, based on microscopical observations, "that the whole brain is permeated by a canalicular lymph-system containing cerebrospinal fluid, the large processes of the neurons lying in lymph-spaces which are continuous with the perivascular lymphatics"<sup>121</sup>

If these observations are true, then dilatation of the perivascular canals by transudate from contained blood-vessels is impossible, since pressure exerted within them would be readily transmitted by the serum to the surrounding tissue and would therefore be everywhere equal and thus prevent such a phenomenon

As a matter of fact there is some evidence to show that the perineuronal lymph-spaces are not so readily permeable as is generally believed. I have met striking lack of success in attempting to perfuse methylene-blue normal saline solution into fresh brains under varying degrees of

118 The shrinkage in the brains of chronic alcoholics may be explained by the noteworthy changes in the ganglion cells of such cases as taught and demonstrated by Dr. Ira Van Gieson many years ago.

119 Quoted by A. E. Russell, p. 1095.

120 Gowers, William R. Abstract of a Lecture on The Nervous System in Old Age, Polyclinic, London, 1907, vi. 131.

121 Mott. Arch. Neurol., London, i. 499.

pressure Whether the apparent impermeability of the brain represents a true finding or whether this failure to demonstrate ready permeability was due to faulty technic or unconsidered factors of capillarity cannot be stated, the technic<sup>122</sup> was similar to that successfully employed by Brodie in demonstrating the permeability of other organs

I shall not consider Mott's production of edema of the brain in animals by experimental ligation of arteries,<sup>121</sup> since his description shows plainly that his conception of brain edema is widely divergent from that held by the Traube school

His reference to the ease with which the perineuronal spaces were made out in some of the cases of experimental anemia<sup>121</sup> is of lessened significance when I remind the reader that these appearances are often due to artifacts Also it must not be overlooked that Huguenin<sup>123</sup> has observed from experiments on animals that a given brain is moister after death than during life

The essential point to be held in mind in connection with the transudate theory is that pressure continuity exists throughout all the fluid molecules in the cranium Pressure caused by transudation from the blood-vessels would be transmitted from molecule to molecule everywhere throughout the cranial cavity and spinal canal—it would be felt, generally speaking, as fully or nearly as much in the subarachnoid fluid on the outside of the brain as in that within the perivascular and interstitial spaces Under these circumstances there would be no disarrangement of the brain, that is to say, no crowding up of the external portions against the bony vault Nor could there be, as already stated, any measurable molecular compression although intracranial pressure were raised to great heights Vascular compression would occur, but this would not explain the soggy condition of the tissues (often considerable from the gross and the histological point of view) intervening between the vascular spaces

On physical grounds therefore we are not justified in maintaining that transudation is a cause of cerebral edema, whatever rôle it may play in the production of edemas elsewhere<sup>124</sup>

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122 Personal Communication

123 Huguenin *Handbuch der speziellen Pathologie und Therapie von v. Ziemssen*, Suppl. Vol., 1878, p. 6

124 The following descriptions taken from autopsy report No. 2,402, are interesting since they show that transudation does not necessarily take place within the skull as a result of thrombosis of the veins of the neck

"Head The longitudinal sinus is free, there is marked pial edema and a moderate amount of fluid at the base The cerebral vessels are everywhere thin and normal The pial veins over both superior convexities are normal with the exception to be noted below The temporosphenoidal and occipital veins on the surface of the right side are the seat of firm, blackish coagula On removing the brain, a large vein with its branches filled with blackish clot is found torn and lying on the superior surface of the petrous portion of the temporal bone This

The old idea propounded by Traube that cerebral edema is due to transudate has persisted with some tenacity in spite of the evidence to the contrary offered by Cannon (1901). With the exception of Cushing (1903 and 1908)<sup>24, 25</sup> it appears that the significance of Cannon's work has been largely overlooked.

Leyden,<sup>125</sup> Duret,<sup>126</sup> Cybulski<sup>127</sup> and Hill<sup>128</sup> all believed that intracranial tension must equal blood tension in order to produce death. Cannon,<sup>129</sup> reasoning from their experiments, in an attempt to explain the mode of death after trauma of the brain, decides that transudation could not raise pressure sufficiently to bring this about, since pressure outside the vessels would not equal that within, owing to loss through resistance of the tissue.

The reader deduces for himself that since the accepted mode of death in cerebral edema is through high tension inducing arterial collapse, the cause of the cerebral edema cannot be transudation.

Cannon develops a theory of edema which differs radically from that of all other observers and in which he ascribes the swelling to osmosis induced by chemical changes in the brain-cells themselves. He finds a satisfactory analogy in the experimental work of Budgett<sup>130</sup> and of Loeb<sup>131</sup> on muscle tissue, and supports his arguments by observations on the capacity of brain tissue when deprived of its blood supply to take up water from a solution isotonic with the blood.<sup>132</sup>

He lays no particular emphasis on causation but points out that Loeb and Budgett emphasized lack of oxygen as a probable cause of the chemical changes in their experiment, and demonstrates the manner in which

vein evidently formed a communication between the above named veins and the lateral sinus. The lateral sinus and the bulb on the right side is the seat of a dark coagulum which is markedly adherent to the wall of the vein. The right middle ear contains an excessive amount of clear fluid. The right mastoid cells appear to be mostly closed, the bone being extremely firm and discolored yellowish. The left middle ear and mastoid normal. Cross section of the brain reveals no gross lesions. There is no edema of the brain substance. The lateral ventricles were not distended and contained a normal amount of fluid.

"Blood-Vessels. The inferior vena cava is normal. The superior vena cava, the right innominate, right and left internal jugular and left external jugular veins are markedly thickened and the seat of an old firmly adherent and partially organized thrombus, which is paler at its cardiac end than toward the head."

125 Leyden, E. *Beitrage und Untersuchungen zur Physiologie und Pathologie des Gehirns*, Arch f Path Anat, 1866, *xxvii*, 519.

126 Duret, H. *Etude expérimentales et cliniques sur les traumatismes cérébraux*, Paris, 1878, p 183.

127 Cybulski, N. *Zur Frage des Gehirndruckes*, Centralbl f Physiol, 1891, *iv*, 834.

128 Hill, L. *The Physiology and Pathology of Cerebral Circulation*, p 168.

129 Cannon. *Am Jour Physiol* 1901, *vi*, 101, 102.

130 Budgett, S. P. *The Similarity of Structural Changes Produced by Lack of Oxygen and Certain Poisons*, *Am Jour Physiol*, 1898, *i*, 210.

131 Loeb. *Arch f d ges Physiol*, 1898, *lxxi*, 47.

132 Cannon. *Am Jour Physiol*, 1901, *vi*, 114, 115.



lack of oxygen would follow as a result of circulatory changes resulting from brain contusion

Cannon's idea that lack of oxygen sets in motion the processes described, while satisfactory from a surgical standpoint, does not seem to apply equally well to other pathological conditions

His theory has the merit that it is the only one so far given that is unassailable from the standpoint of mechanics and I cannot but feel that the process described, or something like it, is responsible for all true cases of cerebral edema, meaning by this edema of the brain as distinguished from pial edema

Cannon<sup>133</sup> suggests a seeming objection to the working out of his theory in the occurrence of fluid noted in the dura or in the ventricles in certain recorded cases, "for why," he says, "does not the fluid pass into the tissues rather than accumulate if the tissues have the great osmotic power attributed to them?" He believes that the question cannot be definitely settled until the osmotic pressure of the fluids has been determined, he adds that the fluids must be encapsulated, and gives the following as a possible explanation

The diffusion of salts from the injured tissues into even a slight amount of fluid in an encapsulated space would render that fluid of higher osmotic pressure than the blood-plasma. The plasma would thereupon pass into the encapsulated space in obedience to osmotic laws and thus increase the fluid in its compressing effect. Further change in the injured tissues would lead to greater swelling in them and to diffusion of more of the dissolved products of decomposition. The diffusion into the encapsulated fluid would still further increase its osmotic pressure, and result in still more plasma coming to increase its volume. Thus there would be a passage of salts from tissues to blood in a series of decreasing concentrations, and a passage of fluids to tissues in a series of increasing osmotic pressures. And since water will pass more rapidly than salts through membranes, the result is usually a greater and greater pressure until death supervenes

The importance of emphasizing Cannon's frank objection to his own theory and his explanation of the same is that if unanswered it affects our own theories and conclusions as well. Such a subdural process as that to which he refers suggests in a way as an analogy, a subdural hydrocephalus—a process in regard to which we know extremely little. Fluid in any amount is so seldom seen post mortem<sup>134</sup> in the subdural space

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133 Cannon *Am Jour Physiol*, 1901, vi, 119

134 Huguenin has discussed this matter rather carefully. It seems curious that some writers have failed to realize that the cranial subdural space is distinct from the subarachnoid space and its spinal prolongation, for, owing to the close apposition of the membranes, at the foramen magnum, there is no subdural space in the spinal canal. To illustrate my meaning, bloody spinal fluid has been considered to be an evidence of middle meningeal hemorrhage, whereas the presence of blood in this fluid in such cases is only an indication of rupture of the dura and subarachnoid membrane or cerebral laceration. In suppurative internal pachymeningitis the cerebrospinal fluid is clear unless there has been an extension of the process to the pia

that we seldom expect to come across anything except the yellowish serous fluid that often accompanies a pachymeningitis hemorrhagica interna. Possibly this fluid may not be so readily absorbed as the normal spinal fluid of the subarachnoid space.

More frequently during life the subdural space seems to contain thin exudate of an apparent inflammatory origin, especially where there is middle ear disease. This exudate, or transudate, may or may not represent the incipient stage of a purulent pachymeningitis and has more than once been described by operating otologists as meningitis serosa. Considering these facts, it seems unwise to attempt to draw any conclusions as to why subdural fluid seems to remain in the subdural space in some cases of apparent brain edema when one might naturally expect that it would be squeezed out.

Cannon's explanation as to the action resulting from the diffusion of salts from injured tissues into an encapsulated space, while theoretically sound for dead membranes, ignores the fact that living animal membranes have a selective action permitting the passage of one ion or molecule and preventing the passage of others, and he also appears to overlook the fact that such diffusion would affect primarily the subarachnoid fluid which directly envelops the brain tissue. We actually do not know the mode of absorption of the subarachnoid fluid nor what relation it bears to the subdural fluid, for experiments thus far conducted have not settled this point. Furthermore, were the resorption of the subarachnoid fluid interfered with, the type of swollen brain described by Traube and Kohlsko could not occur since its change in volume must necessarily be largely at the expense of spinal fluid.

In regard to the occurrence of accumulations of fluid in the ventricles, of which Cannon speaks,<sup>133</sup> several hypotheses may be offered, first, that the cases mentioned were not those of actually swollen or edematous brains, second, that if they were the edema was in its incipience, third, that there was some obstruction to the outflow of spinal fluid from the ventricles. It is conceivable that under certain conditions of acute brain swelling such a result might be brought about. The oft-described permeability of the brain does not always seem to hold good, for cases have occurred in our experience with apparent sudden onset in which flattened dry convolutions, dry cut section and distended ventricles afforded almost proof positive of a confined and increasing ventricular secretion.

A newer theory of edema than that offered by Cannon and one which applies equally well to intracranial conditions is that recently advanced by Fischer.<sup>135</sup> This theory, built on experiments, assumes that certain alterations in the fluids of the body, as for example too great alkalinity

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<sup>135</sup> Fischer, Martin H. The Nature and the Cause of Edema, *THE JOURNAL A. M. A.*, 1908, 11, 830.

or acidity (including excess of carbon dioxid) so increases the affinity of colloids for water that they become swollen with resultant edema and swelling of the tissues. Fischer cites as examples of this action of colloids, swellings due to stings of insects, the swelling of gangrenous tissues when water is applied to them, and the swelling of dead bodies kept in water, as cases in point. The brain is rich in colloidal substances which, should they suddenly begin to absorb water,<sup>136</sup> would increase its volume in such a manner as to force all the cerebrospinal fluid from the skull. A subsequent evacuation of a certain amount of fluid into the tissue spaces of the brain, according to the mechanism described by this writer, would give rise to the soggy appearance observed.

While the type of brain of which I have been speaking is undoubtedly the one which Traube's followers have had in mind in their discussions, it is evident that they have now and then (through oversight of a mechanical principle) confused the swollen edematous brain with the more common form in which there is extensive or moderate pial edema and more or less moisture of the brain substance—the type which has been demonstrated as a physiological or pathological brain shrinkage.

In the first place, although it is impossible for the brain and subarachnoidal fluid to be increased at the same time,<sup>137</sup> certain of the cases are so described as to imply that this may have taken place. In Cushing's article<sup>138</sup> in connection with subtemporal decompression in a case of chronic nephritis which has already been referred to, we are told that there was considerable fluid in the subarachnoid space and that the arachnoid membrane was pricked to allow of this escaping. The obvious deduction on reading Cushing's article is that he was dealing with the

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136 This theory of colloidal absorption is not generally regarded as proved. It is well known, however, that myelin substances are capable of absorbing large quantities of water.

137 Unless we allow the brains in question to have been markedly shrunken beforehand and admit that they have become swollen since. In such cases we can at least be sure that the edema itself could have played no part in the production of pressure symptoms.

138 On page 488 Cushing describes the operation at this stage as follows: "The dura was exceedingly tense and owing to the marked degree of cerebral protrusion that followed the first incision, it was opened with considerable hesitation in the absence of coincident lumbar punctures. It was accomplished, however, without injury to the pia arachnoid. The subdural space contained no free fluid. *The arachnoid on the other hand was markedly distended with fluid* which escaped after pricking the membrane in a number of non-vascular spaces where it bridged the exposed sulci. Not only was there a superabundance of fluid in the arachnoid space but the brain itself appeared soggy and wet." This picture it seems is hardly compatible with our conception of the swollen edematous brain described by Traube unless we accept the paradox that in this instance both brain volume and subarachnoid fluid contents were simultaneously increased. The mechanical complications arising as the result of a subsequent cerebral hemorrhage in the right hemisphere (see page 494 autopsy report of same article) certainly renders the case of little value from the standpoint of the study of cerebral edema.

type of brain which has been especially discussed in this paper, and not with a true case of edema of the brain, as he may have supposed

Similarly Phelps<sup>139</sup> cites a case of a patient dying of traumatic brain injury (the age is not given) in which there was *moderate subarachnoid effusion* and well-marked edema of the brain Cannon<sup>140</sup> cites this case as an example of brain edema To multiply such instances is unnecessary

The conclusion to which we are led, based on the fact that in over 1,000 autopsies taken from the records of the Bellevue Laboratory,<sup>141</sup> there have occurred no truly swollen or edematous brains of the types described either by Kolisko or by Traube, is that these brains are so rare that they cannot figure to any great extent in the common run of those diseases or surgical conditions which they are popularly supposed to accompany and that in many instances the inferences drawn at the autopsy table are incorrect ones based on an improper interpretation of the ordinary appearances of pia arachnoidal collections of fluid, especially where there is also present some widening of the perivascular spaces It must be remembered, in referring to Kolisko's cases, that the number of autopsies which he has performed is enormous

Another type occasionally seen is that in which there is general apparent increase in the volume of the brain, diminution in the size of the ventricles, decreased or absent subarachnoid fluid and pronounced flattening of the convolutions, but in none of these cases has there been any increased moisture from the cut surfaces of the hemispheres On the contrary they have exhibited a rather more than normally dry or glazed appearance<sup>142</sup>

The relations existing between pial effusions and the appearances described as serous meningitis are such as to create confusion This is chiefly because the common milky patches on the arachnoid are apt to be mistaken for active inflammatory processes, while any free fluid made out in the subarachnoid space is consequently assumed to be serous unless it is slightly cloudy<sup>143</sup>

A critical review of the literature of serous meningitis leads one to the conclusion that a great deal has been written on the subject which will not bear analysis, indeed, such an examination causes one to question whether, taking into account the various possibilities of mistake, the

139 Phelps Traumatic Injuries of the Brain and Its Membranes, vi, 536

140 Cannon Am Jour Physiol, 1901, vi, 97

141 Dr Norris tells me he has never observed this condition, although he has for four years been on the watch for it

142 A case of this sort is included in our tables of cranial weights and volumes, note Group II, Accession No 2,099, Table 5

143 In such cases a careful bacteriological examination must be made to eliminate a beginning inflammatory process, especially in pneumonia

disease can be said to have been positively demonstrated Thiemich<sup>144</sup> observes that "the term serous meningitis is primarily anatomical and as such is ambiguous," a statement the truth of which becomes increasingly apparent with added study The instability of the foundations on which the study of the subject of serous meningitis has been made to rest is made apparent when one analyzes the fourteen cases on which Quincke<sup>145</sup> based his clinical observations The first six cases were entirely clinical lasting up to five months with acute onset, acute course and recovery No bacteriological work was done A second group described as "acute cases with a chronic course," comprises three cases Two of these came to autopsy and showed chronic internal hydrocephalus with tuberculosis elsewhere in the body.

In a third group comprising five cases and described as "chronic," three came to autopsy The first of these showed a granular ependymitis with hydrocephalus internus and no tubercles The second showed chronic hydrocephalus, ventricles very wide and filled with clear fluid, a granular ependyma, meningitis, extensive milky clouding of the pia, and slight opacity of the membranes of the cord There was a large abscess in the pelvis, pyemic abscesses in the lungs, an old endometritis, and "myelitis (?)" No bacteriological examination was made In a third case enormous hydrocephalus (800 cc of fluid) was present For the entire group no histological findings are recorded, no bacteriological work was done, and intracranial pressure was measured only five times Every case of Quincke's, therefore, which came to autopsy, was a case of internal hydrocephalus It is hard to see on what grounds he based his assumption that in these cases the causative factor was a serous inflammation of the meninges At the same time Quincke<sup>146</sup> informs us that "he did not find that the fluid in chronic serous meningitis differed from ordinary cerebrospinal fluid Believing as I do that the spinal fluid is a ventricular secretion,"<sup>147</sup> I cannot see how his point is demonstrated or how he differentiates his cases from the ordinary form of internal hydrocephalus

Thiemich, as already noted, looks on the so-called acute hydrocephalus of childhood as a ventricular serous meningitis He considers that the fluid of "internal" serous meningitis is usually clear but that there are slight changes which indicate inflammation of the choroid plexus and ependyma<sup>148</sup> Possibly the terms "choroiditis" and "ependymitis" are more suitable here

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144 Thiemich, *Serous Meningitis in Diseases of Children*, p 413

145 Quincke *Samml klin Vortr*, pp 656 668

146 Quincke *Samml klin Vortr*, p 678

147 The reader is referred to Brodie's Harvey Lecture, New York, 1909, on Renal Activity (the choroid plexus being supposed to functionate as do the glomeruli)

148 For composition of the fluid in hydrocephalus, see under spinal fluid, *Text-Book of Physiological Chemistry*, Hammarsten Ed, 1908, p 264

Quincke makes a statement in his article that has a distinct mechanical significance, he says "In general venous stasis (as in valvular heart disease) we see, in addition to edema of the brain substance, increase in fluid not only in the ventricles but also, and usually in a higher degree, in the subarachnoid space, whereas local venous stasis leads only to transudation into the ventricles with transudation into the brain and compression of the convolutions against the skull "

Edema of the brain substance with increase in the ventricular and subarachnoid fluids is obviously a mechanical impossibility as already pointed out The second statement implies a closure of the iter or foramina of Magendie

Boenninghaus' series is equally as unsatisfactory as Quincke's It is observed that most of his cases can readily be accounted for as either the beginnings of acute purulent or epidemic cerebrospinal meningitis, or as the chronic and partly healed phases of the same conditions

It is hard to see how the condition can be demonstrated by the histological findings when we consider that the only way one can really prove that a given case of meningitis is serous in character and not some form of leptomeningitis with brain shrinkage, is by the presence of serous exudate

Thiemich lays great emphasis on the bacterial, microscopical, and chemical examination of the spinal fluid in these cases and it seems safe to say that this is the only satisfactory method in making a diagnosis

#### *PART 4—THE CLINICAL SIGNIFICANCE OF PIAL EDEMA*

There are one or two points of importance that require consideration before closing Of these the first to be considered is the question of the extent to which high intracranial pressure accompanies pial edema

The simplest method of estimating intracranial pressure post mortem, as has already been stated, is by observation of the tenseness and bulging of the dura just after the skull is opened Although only a rough guide, this method may be regarded as accurate enough for present purposes In twenty-eight consecutive cases of pial edema examined, the dura was found tense in ten, indicating that high intracranial pressure coexisted with pial edema in more than one-third of the cases Proof that the two conditions do not necessarily coexist is furnished by a case of pial edema which was tapped several hours before death by Dr. H V Guile, former intern of the Bellevue Hospital staff The intracranial tension, as measured by him, was normal (150 mm of H<sub>2</sub>O)<sup>149</sup> Certain writers on alcoholism, including some recent ones, have looked on the presence of pial

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<sup>149</sup> See Accession No 2,057, in Table 5

edema as evidence of high intracranial tension, it seems wise in this connection to point out that in many cases symptoms which may have been due to coexistent high intracranial pressure were wrongly ascribed to a "wet-brain" found post mortem

The second question worthy of attention is, May pial edema be looked on as a cause of symptoms? I have been at some pains to question the various house physicians as to the ante-mortem condition of the cases on which I performed the head autopsies, particularly those cases in which much edema was present. In Table 5 are the results obtained by this system of inquiry

I give here a report of all cases as they occurred regardless of whether or not edema was present, but regrouped for convenience of study

TABLE 5—REPORT OF ALL CASES AS THEY OCCURRED

## GROUP 1

Acc No	Degree of Edema	Disease	Mental Condition Just Before Death
2,039	XXX	Tuberculous meningitis	Stupor present
2,057	XX	Brain tumor	Stupor present, (intracranial tension ante-mortem was 150 mm of H <sub>2</sub> O)
2,085	XXX	Congenital diplegia	Torpid from birth
2,111	XX	Uremia	Uremic coma
2,152	X	Tuberculous meningitis	Stupor present

In this group are placed those cases in which the nature of the lesion is such that it would be difficult to determine the relation of stupor to the coexisting edema. Case 2,057, mentioned above, is of particular interest as suggesting that stupor with brain tumor is not necessarily dependent on high intracranial tension, as the tension in this case is normal

## GROUP 2—NO PIAL EDEMA PRESENT

Acc No	Degree of Edema	Disease	Mental Condition Just Before Death
1,907		Chronic pulmonary tuberculosis	No cerebral symptoms
1,959		Delirium tremens	Delirious till death
1,974		Polyserositis	No cerebral symptoms
2,099		Fatty liver, cause of death unknown, infant	Convulsions
2,109		Pulmonary tuberculosis	No pressure or other cerebral symptoms
2,146		Carcinoma of stomach	No cerebral symptoms

The cases in this group have been included merely for the sake of completeness

Of the following eighteen patients, nine had absolutely no symptoms of cerebral disturbance. Five were irritable or delirious, and four stuporous or comatose. Of the four cases last mentioned, two presented the picture known as "alcoholic wet-brain," a third was profoundly stuporous and a fourth comatose. Although included in this group, it is obvious

that coma in a case of perforated gastric ulcer with fatal hemorrhage (Acc No 2,133) might readily be due to other factors than those caused by pressure of fluid on the cortex

GROUP 3 —CASES SUITABLE FOR STUDY OF THE RELATION OF PIAL EDEMA TO SYMPTOMS OF STUPOR OR COMPRESSION

Acc No	Degree of Edema	Disease	Mental Condition Just Before Death
1,879	XX	Cirrhosis of liver	No evidence of cerebral disturbance
1,880	XXX	Interstitial pneumonia	No signs of cerebral compression
1,891	XXX	Ac par nephritis	Had no cerebral symptoms until just before death, when he became slightly delirious and later sank into a stupor about which there was nothing characteristic
1,892	XXX	Epithelioma of esophagus	Died in delirium
1,903	XX	Chronic cardiovascular disease	Was never comatose, nor did he have any mental symptoms beyond the irritability common to advanced alcoholics
1,912	XXXX	General arteriosclerosis	Characteristic mental symptoms of senility
1,963	XX	Cardionephritis	No cerebral symptoms
1,964	XXX	Carcinoma of esophagus	No cerebral symptoms
2,052	XXXX	Chronic interstitial nephritis	Stupor was present
2,082	XX	General miliary tuberculosis	No cerebral symptoms
2,113	XX	Chronic alcoholism, gangrenous cervicitis	Died in delirium
2,112	XX	Landry's paralysis	Conscious till death
2,117	X	Chronic glomerular nephritis	No cerebral symptoms
2,133	X	Perforated gastric ulcer	Died in coma
2,147	XXX	Pulmonary tuberculosis, chr alcoholism	Irational, wandering and partly stuporous for some time before death
2,148	XXX	Pulmonary tuberculosis, chr alcoholism	Moderate degree of stupor present
1,949	XX	Secondary hemorrhage	No cerebral symptoms
2,153	XXX	Emphysema	Rational all the time, died suddenly on attempting to sit up in bed

On review, there appears in these findings no evidence in support of the idea that pial edema is in itself a producer of symptoms. The symptoms of delirium tremens and "alcoholic wet-brain," it should be remembered in this connection, have been ascribed more properly by others to toxemia. My observations thus have led me to believe that such symptoms as have been recorded are the result of high intracranial pressure or toxemia (CO<sub>2</sub> or other poisons), or both, coexisting with pial edema, but not otherwise related to it.

#### CONCLUSION

My conclusions may be summed up as follows

- 1 The collection of fluid in the pia mater is not *per se* a pathological process but in every instance represents the reciprocal of brain shrinkage
- 2 It produces *per se* no symptoms
- 3 Thickenings of the meninges in such cases take place chiefly in the arachnoid and are not to be regarded as representing a true inflammatory process



4 The brain increases in size up to puberty and diminishes thereafter proportionately to its diminution in weight, as shown by comparison with the tables of brain weights presented

5 Increase or diminution in size of the brain is not determined by the state of nutrition of the rest of the body

6 The appearance of "wet-brain" so called, or pial edema of alcoholics, is due to brain shrinkage and has no pathological significance *per se*

7. The appearances of pia-arachnoidal effusion are readily mistaken for those of serous meningitis

8 When a collection of fluid is present in the pia arachnoid, a diagnosis of edema of the brain is open to question and can be made only on the assumption that the brain has been previously in a more shrunken condition

9 We see no reason to believe that transudation can be a causative factor in the production of cerebral edema

10 Cases of swollen or edematous brains with dry pias are decidedly uncommon at autopsy and the diagnosis of cerebral edema should be made only when actual increase in the volume of the brain matter can be proved

I wish to thank Dr Charles Norris for the opportunity to carry out these investigations and for his extended cooperation and criticism. I also wish to thank Drs A M Pappenheimer and Cyrus W Field of the laboratory staff for assistance and criticisms, Dr Ernest Sachs for a critical review and Mr Albert L Stillman for an exposition of those principles of mechanics and physics that are involved in this paper

128 Lexington Avenue

# A CLINICOPATHOLOGICAL STUDY OF PRIMARY CARCINOMA OF THE LIVER

HOWARD T KARSNER, M D  
PHILADELPHIA

Although much had been written previously, the work of Hanot and Gilbert<sup>1</sup> was the first comprehensive investigation of primary carcinoma of the liver and marked a distinct epoch in the study of the disease. Numerous contributions followed this before the publication of Eggel's<sup>2</sup> great work, the most notable in the interim being that of Siegenbeek van Heukelom<sup>3</sup> whose brevity, clearness and penetrating logic demonstrated a most comprehensive grasp of the subject.

It is not my purpose to go into the details of the voluminous literature on primary carcinoma of the liver, for the works mentioned are most painstaking in this respect. Furthermore some of the more recent essays on the subject bring the literature completely up to date, among these works should be mentioned the writings of Conti,<sup>4</sup> Fulci,<sup>5</sup> Bertelli,<sup>6</sup> Theodorow,<sup>7</sup> Ribbert,<sup>8</sup> Cruickshank and Teacher,<sup>9</sup> and of Fabiani.<sup>10</sup>

In order to have some standard for judgment I have accepted Eggel's conception of the clinical and pathological features of the disease, for although several years have passed since the appearance of his paper, very little is to be added to his description. After reviewing the literature of the nomenclature of epithelial tumors he includes under the broad term of carcinoma all epithelial new growths of malignant character, a thoroughly German conception. In reference to the liver, he speaks of carcinoma when there is either macroscopically or microscopically the formation of tumor thrombi or metastases or when there is exhibited a destructive influence on the surrounding liver tissue.

On the basis of Eggel's critical study of 163 cases from the world's literature it may be said that cancer of the liver is most frequently a

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\*From the McManes Laboratory of Pathology, University of Pennsylvania

\*Read before the Pathological Society, Philadelphia, May 26, 1910

1 Hanot and Gilbert *Etudes sur les maladies du foie*, Paris, 1888

2 Eggel *Beitr z path Anat u z allg Path*, 1901, *xxx*, 506

3 Siegenbeek van Heukelom *Beitr z path Anat u z allg Path*, 1894, *xvi*, 341

4 Conti *Policlinico*, Rome, 1908, *xv*, 385

5 Fulci *Policlinico*, Rome, 1908, *xv*, 408

6 Bertelli *Riforma Med*, 1908, *xxiv*, 957

7 Theodorow *Virchow's Arch f path Anat*, 1908, *cxciii*, 407

8 Ribbert *Deutsch med Wchnschr*, 1909, p 1607

9 Cruickshank and Teacher *Jour Path and Bacteriol*, 1910, *xiv*, 282

10 Fabiani *Gaz d osp*, 1910, *xxx*, 433

disease of men (63.3 per cent males, 36.7 per cent females) occurring particularly between 50 and 60 years of age (average for men 53.11 years, for women, 52.23 years). The past history of the patient often shows factors that would seem to favor cirrhosis, such as alcoholism, syphilis, biliary calculi, trauma and in a few cases (four in 163) a history of cancer in other members of the patient's family.

Clinically, the earliest symptoms are those of more or less vague trouble in the gastro-intestinal tract. Before the appearance of the symptoms referable to cancer, symptoms of atrophic cirrhosis sometimes predominate. After the development of the cancer, loss of flesh, digestive disturbance and cachexia put in their appearance. Statistically the 163 cases show icterus in 61 per cent, ascites in 58.5 per cent, edema, especially of the lower extremities, in 41 per cent, splenic tumor in 32 per cent and fever in 14 per cent. The duration averages about six months, although the estimation of the time of origin is much confused by the symptoms of the early cirrhosis.

From the point of view of gross morbid anatomy Eggel differentiates three forms of primary carcinoma of the liver.

1 The nodular form. The new growth appears in the form of nodules of variable number and size, for the most part clearly separated from the liver tissue.

2 The massive form. The tumor forms a large mass taking in an entire lobe or the greater part of it, is poorly defined and often shows smaller metastatic nodules.

3 The diffuse form. The whole liver is infiltrated with numerous small tumor nodules often no larger than an acinus, each enclosed in a connective tissue band so that the liver often is only differentiated from a pure cirrhosis by the aid of the microscope.

This grouping differs from the generally accepted classification of Hanot and Gilbert only in the third form, which the latter authors term *cancer avec cirrhose*. Cirrhosis is such a common feature in cancers that should properly be classified as nodular or massive, that in the light of more modern studies of a greater number of cases, this classification of Hanot and Gilbert seems unjustified.

Microscopically there are two chief groups, the carcinoma solidum (really a carcinoma simplex) and the carcinoma adenomatosum, corresponding respectively to the *épithéliome alvéolaire* and the *épithéliome trabéculaire* of Hanot and Gilbert.

Although Hanot and Gilbert thought it possible to differentiate these forms clinically, the studies of Eggel and others seem to indicate the impracticability of such a fine diagnosis.

The purpose of the present communication is to present a detailed study of nine cases of primary carcinoma of the liver, some of which came under my personal observation in the Philadelphia General Hospital.

and the University Hospital, and others of which were kindly referred to me by Dr Warfield T Longcope, the Director of the Ayer Clinical Laboratory of the Pennsylvania Hospital. The special features of these cases will be discussed with their individual presentation. The gross descriptions of the specimens from the Pennsylvania Hospital are by Dr Longcope. The minute descriptions throughout are my own.

#### REPORTS OF CASES

**CASE 1—History**—M W, a white woman, aged 40, was a patient in the University Hospital (No 1,885) in the service of Drs Martin and Carnett. The clinical history is abstracted as follows. The family history is negative. Eighteen years ago the patient had an attack of chills, fever and jaundice with vague pains in the abdomen, she had similar attacks about once a year from this time on, and the most of these had the same symptoms with loose light colored stools. She never vomited but often felt nauseated. Seven years ago she had an attack of inflammatory rheumatism which lasted four weeks. She has been an excessive coffee drinker.

**Present Illness**—Three months ago the patient was taken with an attack of chills, fever and jaundice, the last being much deeper than ever and remaining unchanged up to the present time, has much diarrhea, has lost weight and complains now of pain and tenderness in the upper abdomen, especially on the right side.

**Physical Examination**—Jaundice and emaciation are present and the liver is markedly enlarged, easily palpable, as is also the case with the spleen. Temperature is not elevated at any time. Urine shows slight sediment, 1018, acid, negative for albumin, sugar, but positive for bile, it shows a few leukocytes and epithelium.

Blood—Hemoglobin, 71 per cent, red blood cells, 3,910,000, white blood-cells, 7,900. Differential count, polymorphonuclears, 70 per cent, lymphocytes, 12 per cent, large mononuclears 1 per cent, transitionals, 9 per cent, eosinophils, 6 per cent, basophils, 2 per cent. No malarial organisms.

Stools show no free fat, but a few fatty acid crystals, a few small masses of soap.

Exploratory operation was performed by Dr Martin after which there developed a very marked hemophilic condition and the patient died a few days later.

**Necropsy** (by H T K)—This was performed about twelve hours after death. The notes are abstracted as follows. Liver weighs 2,320 gm, measures 28 by 23 by 7.5 cm, shows prolongation of the sharp anterior edge, the edge itself is of normal sharpness. The upper surface is flattened. The capsule is adherent posteriorly and there are several glands adherent but not very densely, in the transverse fissure. The surface of the liver is coarsely granular but, except in the position of adhesion shows a glistening surface. The color is generally green with mottlings of yellow and yellowish-gray areas approximating the size of a millet-seed to that of a small pea, consistence is greatly increased. On section the liver cuts with considerably increased resistance, cut surface shows the same degree of granularity as noted on the outer surface. In a few areas tubules with very much thickened yellowish gray walls are seen to be cut across. Approaching the under surface of the right lobe one finds on cross-section a mass running almost directly anteroposteriorly, apparently spindle shaped, extending from the anterior margin of the liver almost all the way through it, but not being visible on the surface except anteriorly where a small area of triangular shape is seen, which superficially resembles scar tissue. A cross section of tumor mass in its middle part measures 5 by 3 cm, it tapers posteriorly to become invisible, while anteriorly it measures roughly 2 cm in diameter. Direct connection of one part of this mass with other parts all through the liver sub

stance cannot positively be demonstrated. The mass is not sharply outlined and fades away into the hepatic tissue with almost no signs of pressure, apparently replacing the parenchyma. The tumor is grayish-yellow in color with some pin-head points centrally placed of a deep yellow color with a peripheral zone of hemorrhagic points varying from bright red to a deep blue color. The consistence of the mass is somewhat firmer than that of the liver tissue and approximates that of hard rubber, the central minute yellowish areas are considerably softer and are probably minute areas of necrosis. The number of ducts with thickened walls (same hard consistence as tumor) is greater in the neighborhood of the tumor than in other parts of the liver, but can be demonstrated generally in both right and left lobes.

The condition of the other organs is indicated in the gross anatomical diagnosis as follows. Primary carcinoma of liver, metastases to subhepatic glands and right adrenal, general jaundice, ascites, splenic tumor, chronic diffuse nephritis, general abdominal congestion, laceration, erosion of cervix uteri with hemorrhage into wall, chronic adhesive perioophoritis (left), chronic cystic oophoritis (right), edema and congestion of lungs, very slight cloudy swelling of myocardium. Microscopically, three sections from the liver were studied, one of liver, two of tumor. The liver proper shows marked thickening of the capsule or Glisson made up of moderately dense fibrous tissue without many nuclei but considerably infiltrated with round cells. In many places the capsule is infiltrated with epithelial cells of the type of those found in the tumor, i. e., large, generally circular vesicular nuclei and moderately abundant, well-stained protoplasm. Many epithelial tubules are seen on cross section which either appear as normal gall-ducts, or show several irregular layers of epithelium without distinct basal membrane. Some of the larger bile ducts show distinct peripheral fibrosis. The blood-vessels are normal. In many areas the peripheral parts of the lobule show distinct replacement of the liver cells by irregularly placed cells of the type seen in the tumor. The parenchymal cells are swollen, granular and show loss of outline although the general chain arrangement is maintained. Many of the cells contain masses of granular greenish-yellow pigment which in some cases is so abundant as to completely occupy the cell. In many cases large collections of pigment are found in spaces corresponding to bile capillaries. The nuclei are generally normal, some few, however, stain poorly and show abnormal arrangement of chromatin. Duplication of nuclei in a cell is observed but no mitotic figures. Central veins show no congestion.

The tumor proper is richly fibrous and is made of irregularly arranged intercommunicating acini, lined sometimes by a single layer, sometimes by multiple layers of epithelial cells. These are low columnar cells, morphologically and tinctorially like bile duct epithelium, often, however, being of somewhat larger size. The nuclei, frequently, are more highly vesicular than in normal ducts and mitotic figures are fairly frequent. The growth penetrates through the liver tissue irregularly, in places substituting itself for liver tissue and in other places pushing the tissue aside. Numerous areas show fine hemorrhages. There appears to be every transitional stage between simple bile duct proliferation and the adenocarcinoma. Extension into veins occurs but is not frequent, the tumor even here shows the adenomatous arrangement and often completely obliterates the vessel. Involvement of lymph-spaces could not be determined.

Other tissues were examined microscopically, the diagnosis being Primary adenocarcinoma of the liver, with involvement of the liver veins, cloudy swelling of myocardium, chronic congestion of spleen, chronic interstitial nephritis with superimposed acute parenchymatous nephritis.

To summarize, the tumor appeared in a woman 40 years of age. Clinically she had a history of excessive coffee-drinking, and an illness simulating cholelithiasis. She showed jaundice, emaciation, and very slight ascites. Pathologically the tumor was primary in the liver, with limited

metastases, slight neoplastic thrombosis, cirrhosis and splenic tumor. The liver tumor is of the tubular type and apparently has its origin in the finer bile-ducts.

**CASE 2—History**—C. C., a Swedish man, aged 49, was a patient in the Philadelphia General Hospital (No. 2,450) on the service of Dr. H. B. Allyn. The clinical history is abstracted as follows. The chief complaint is weakness in both legs. The family history is negative. The patient had the usual diseases of childhood, had pneumonia, had lead colic five years ago. He does not use alcohol, denies venereal infection. He is a lead worker. The present illness began with pain in the abdomen, weakness and constipation one week ago.

**Physical Examination**—This shows blue line on gums, arcus senilis, unequal pupils, enlarged liver (3 cm. below costal margin) and later demonstrable ascites. Before death he developed convulsions, hematemesis, delirium.

**Blood** Hemoglobin, 40 per cent, erythrocytes, 3,230,000, leukocytes, 5,000, of which the polymorphonuclears formed 76 per cent, small lymphocytes, 9 per cent, large lymphocytes, 8 per cent, eosinophils, 3 per cent, basophils, 4 per cent. No basic degeneration of erythrocytes.

**Urine** Alkaline, specific gravity, 1.018, negative for albumin and sugar.

**Necropsy**—This was performed by me twenty-four hours after death, the notes being abstracted as follows. Liver weighs 3,300 gm., measures 28 by 23 by 11 cm., very firm, abnormally rounded, shows a smooth, glistening, transparent capsule through which the liver substance is seen to be studded with innumerable grayish-yellow nodules with umbilicated surface, generally rounded, discrete and confluent, varying in size from a diameter of 1 mm. up to 4 cm. The organ cuts with moderately increased resistance, shows the same appearance of discrete and conglomerate nodules, showing a central mass of bright yellow structureless apparently necrotic material sharply outlined, and surrounded by a linear pearly gray mass generally about 2 mm. in thickness, this latter mass, although sharply outlined from the central necrosis, is not sharply defined from the liver substance and shows a tendency to diffuse itself through the liver substance following in a general way the lines of the capsule of Glisson. In some places suggestions of liver structure are still found within the central necrotic masses and some of these also show small areas of hemorrhage. The uninvolved liver tissue is very small in amount and shows well-marked central congestion and greenish-yellow discoloration of the peripheral zone.

The other organs correspond in appearance to the gross anatomic diagnosis. Primary nodular carcinoma of liver with metastases to lungs, pleuræ, pancreas, left kidney, retroperitoneal lymph-nodes, congestion and edema of lungs, ascites (4 liters), anemic infarcts of spleen and kidneys, acute vegetative mitral and aortic valvulitis, chronic interstitial nephritis, arteriosclerosis.

Microscopically the description of the liver is the composite of five slides. Capsule thickened by an overgrowth of dense fibrous tissue. The capsule of Glisson shows well-marked fibrous tissue overgrowth and some lymphocytic infiltration. The veins are moderately congested and the arteries show slight thickening of their walls. In numerous places where there is especially marked overgrowth of the fibrous tissue an epithelial proliferation is noted. The epithelial cells are columnar type and are arranged in the form of irregular tubular or acinous masses, either solitary or continuing to form large infiltrating areas. In one slide the cells correspond very closely to those of the bile ducts, being low columnar, only moderately acidophilic, and with relatively small, circular, slightly vesicular nuclei. In studying the sections considerable variation is noted in the character of the epithelial cells of the proliferating masses, those showing most marked change being of high columnar type, with suggestions of cilia, faintly stained protoplasm and vacuoles which, although usually small and poorly defined, contain a finely granular basically stained substance evidently mucinous in nature. Much of the epithelium of this type is mounted on thin villous strips of

connective tissue In the places where the cells present a less markedly columnar element there can be found occasional figures, which present the same type of proliferation as that seen in the coccidiosis of the rabbit's liver—a surrounding band of connective tissue and a distinct villous proliferation of the lining epithelium The tumor as a whole shows few karyokinetic figures The lumina of the acini are more or less filled with slightly acidophilic granular material and fragments of nuclei, in some instances also complete desquamation of the cells, the supporting connective tissue is scanty Evidences of infiltration are numerous Piling up of cells along the walls of the acini and definite penetration of the basement membrane are seen commonly Penetration of the mass through the liver substance replacing connective tissue and substituting itself for parenchymal tissue is a common feature Necrosis is found in several sections, apparently as a central change, the necrosing areas being surrounded by proliferating epithelial tissue Small areas showing neoplastic thrombosis of the perilobular veins are observed but they are relatively infrequent

The lobules not involved by the cancer show swelling of the parenchymal cells, obliteration of outline, obscuration of the nuclei and protoplasmic granularity The nuclei are vesicular but variable in size, some being much enlarged and showing increased chromatin content Many of the central lobular cells show minute vacuolization, associated with slight nuclear pyknosis and some hemosiderin pigmentation Fibrosis about the central vein can be seen but no congestion is noted

Other organs were examined microscopically and the diagnosis is as follows Primary adenocarcinoma of liver with neoplastic thrombosis of veins, passive congestion, edema, tumor metastases of lung, slight chronic interstitial myocarditis and infarct of papillary muscle, chronic fibrous splenitis and perisplenitis, anemic infarct of spleen, subacute parenchymatous nephritis, anemic infarct, tumor metastases, slight vacuolation and chromaffine increase in adrenals, tumor metastases of lymph-node

To summarize, this tumor appeared in a man 49 years of age Clinically there is a history of lead-poisoning (lead worker), short duration of illness, ascites, enlarged liver, abdominal pain (possibly lead colic) but no jaundice Pathologically the tumor is of the nodular type with very little cirrhosis, histologically adenomatous, with slight neoplastic thrombosis and wide-spread metastases outside the liver

CASE 3<sup>11</sup>—*History*—The patient, E F (No 2,128), was a girl aged 11, white, Section was submitted to the laboratory through the State Department of Health by Dr H Y Pennell, of East Downingtown, Pa Dr Pennell in a letter gave the following history, which has been abstracted The patient was of exceptionally robust stock, the history being otherwise negative She had always been strong and healthy except for an attack of pneumonia eight years ago

*Present Illness*—This began early last summer The patient consulted a physician in June, 1907, and following months for jaundice This (jaundice), with loss of energy and disinclination to work or play or walk far, was the chief symptom, until within the last two or three months It was recently noticed that she had become unnaturally stout and so weak that she could with difficulty go upstairs She complained of no pain excepting over the heart on exertion

*Physical Examination*—This showed cachectic pallor, moderate jaundice, ascites, distention of abdominal veins, hypertrophied heart, dyspnea, anasarca The temperature ranged between 99 F and 103 F, pulse about 130, respiration

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<sup>11</sup> This case was used by me in a paper on Carcinoma in Early Life, New York Med Jour, 1909, xc, 1109

about 34. Feces were pale, urine negative for albumin and sugar. Blood examination failed to show leukocytes. Constant systolic apical cardiac murmur.

*Necropsy*—This was limited to the abdomen, and was performed by Dr Pennell, whose notes are abstracted. "On opening the median line of the abdomen the first thing met was the enlarged spleen, about the size of a normal liver, very dark and uniform in color, soft and smooth. The liver was next investigated and found to be of a brownish yellow color, a little smaller than normal, very hard, and containing on the surface and within the substance innumerable tumors, of size from those just visible to that of a walnut. The larger ones showing radiations from umbilicated centers. It was a portion of one of these sent for examination. The gall-bladder was empty, normal in size, but almost pure white in color. The stomach and bowels, as also both kidneys and pancreas, appeared to be normal. There was no tumor in the pelvis. I regret not having examined the heart and mediastinum, but was convinced at the time that we had the primary seat of trouble in the liver."

Histologically, the section of liver showed the perilobular connective tissue much increased and the seat of numerous fibroblastic and other early cellular elements indicating the progressive character of the cirrhotic feature of the case. All through this tissue were found small biliary tubules, and scattered in the structure were small, isolated groups of hepatic cells which had been cut off from the lobules by the invading connective tissue. In addition there were scattered numerous smaller epithelial cells of the type of the bile ducts, both as isolated cells and in more or less broken columns. The fibrous tissue penetrated to some extent into the hepatic lobules, but in very irregular manner and degree.

The hepatic tissue showed a variable state, at places (generally rather toward the periphery than center of the lobule) it was definitely necrotic or showed fatty degeneration. Much showed a minor grade of fatty infiltration, and much was practically unchanged. No pigmentary deposits were noted, either in the liver cells or in the perilobular tissue.

The general appearance was that of an adenocarcinoma, apparently quite diffuse, and accompanied by a progressive cirrhosis.

The spleen showed congestion and edema.

To summarize, this tumor appeared in a girl aged 11, whose history is negative. She showed a short duration of disease, jaundice, ascites, edema clinically, and a nodular adenocarcinoma of the liver with cirrhosis but without venous involvement or apparent metastasis.

*CASE 4—History*—F. W., a white man, aged 53, an American, was a patient in the Philadelphia General Hospital (No. 2,518), on the service of Dr. Henry. The clinical notes are abstracted as follows.

The chief complaint is pain and tenderness in the epigastrium. The family history is negative. The patient had the usual diseases of childhood, he used tobacco excessively, never used alcohol to excess. The present illness began with pain and tenderness in epigastrium two months before admission. The patient had hemoptysis occasionally.

*Physical Examination*—This shows slight jaundice of upper part of body, dilated veins of chest, nodular enlargement of liver, ascites, splenic enlargement, edema of feet.

Blood. Hemoglobin 70 per cent, erythrocytes, 3,560,000, leukocytes, 8,800, of which polymorphonuclears formed 67 per cent, small lymphocytes 26 per cent, large lymphocytes 1 per cent, eosinophils, 4 per cent, basophils, 2 per cent.

Urine. Acid, specific gravity 1.026, shows erythrocytes and epithelial cells, negative for albumin and sugar.

Stools. negative for occult blood.

The patient died of erysipelas.



*Necropsy*—This was performed by me thirty six hours after death, the notes being abstracted as follows. Liver weighs 2,700 gm, measures 31 by 18 by 9 cm, surface markedly irregular and nodular, deeply blood-stained and markedly adherent to the omentum, which is folded over the surface of the liver. Through the capsule many of the nodules have a yellow appearance and others show a dark red color, none show umbilication. Organ cuts with increased resistance and in the right lobe it measures only 12 cm in coronary diameter, shows a well-marked atrophic cirrhosis, there being present a dense network of fibrous tissue in whose meshes are circular masses of slightly projecting greenish brown liver substance. The left lobe is enormously enlarged in all its diameters and shows little remaining liver tissue. Cross-section shows necrotic nodules varying from a diameter of 1 mm up to 5 cm, the edges are not sharply outlined and tend to fuse with irregular bands of connective tissue about them. These nodules, which show red through the capsule, appear to be made up of a small network of distended vessels.

The other organs showed the appearances indicated in the gross anatomical diagnosis. Chronic adhesive pleurisy, passive congestion and edema, tumor metastases, of lung, cloudy swelling of myocardium, sclerotic mitral and aortic valves, primary cancer, with atrophic cirrhosis of liver, acute splenic tumor and chronic fibrous perisplenitis, arteriosclerotic chronic interstitial nephritis, chronic atrophic gastritis, congestion of gastro-intestinal tract, ascites, arteriosclerosis, tumor metastases to mediastinal, retroperitoneal and mesenteric lymph-nodes.

Microscopically several sections of liver were examined. The outer capsule and peribular connective tissue are considerably overgrown and show slight infiltration with lymphocytes. The overgrowth is so marked that the acini of the liver appear as small isolated masses scattered irregularly throughout. The liver-cells show cloudy swelling and in the center of the lobule considerable atrophy. The central veins are moderately congested. Marked bile duct proliferation is evident throughout. The veins of the peribular tissue are considerably congested and show frequent neoplastic thrombosis.

The tumor is made up of low columnar and irregular cells approximating the size of those of the bile ducts, and the staining reactions of the protoplasm are closely similar. The nuclei are small, vesicular and very like those of the bile-ducts. Mitotic figures are very infrequent. For the most part these cells are arranged in fairly large nests with ramifications into the surrounding tissue in the form of small finger-like projections. The cells in the margins of these masses are well preserved, but there is very evident central necrosis and frequent microscopic hemorrhage into these necrotic areas. The invasion of the veins is very well marked, the vessels being completely occluded by the thrombotic masses and showing some stretching of the muscular and elastic tissues of their walls. Connection between the larger masses and the proliferated bile ducts is not very clear but transition stages can be demonstrated with great facility. The finer grouping of the cells of the larger masses is not clearly adenomatous because of the fact that, although the cells are arranged in little circles, yet distinct lumina are infrequent. However, the grouping of the cells and their apparent connection with, and close similarity to, the proliferated bile-ducts seems to justify the diagnosis of tubular adenocarcinoma.

Sections of other organs were made, the microscopic diagnosis being Primary adenocarcinoma of liver with marked sclerosis and neoplastic thrombosis, metastasis to diaphragm, lungs, lymph nodes (mediastinal), passive congestion, edema of lungs, leukoplakia of tongue, chronic interstitial splenitis, pancreatitis, nephritis, fibrosis and chromaffin increase in adrenals.

To summarize, this tumor appeared in a man 53 years of age. The history shows excessive use of tobacco, short duration of illness, ascites, hemoptysis (?), dilated veins of chest, nodular enlargement of liver.

splenic enlargement, ascites, edema of feet and slight jaundice. Pathologically, the tumor is notable for its marked fibrosis associated with general cirrhosis elsewhere. The tumor is nodular in type, glandular microscopically, shows neoplastic thrombosis, moderately rich metastasis and associated splenic tumor.

**CASE 5—History**—The patient, J. K., a white man, aged 52, American, was in the service of Dr. Stengel in the Pennsylvania Hospital (No. 1,154). The records and specimens were furnished me by Dr. Longcope. A brief abstract of the clinical history follows. The chief complaint is pain in abdomen. Past history is negative, except for alcoholism.

**Present Illness**—Symptoms began four months ago with cramp like pains in abdomen. Three weeks ago the patient became jaundiced and began to vomit, he had constipation and clay colored stools, there was no blood in stools or vomitus. The abdomen increased rapidly in size. Recently the legs were edematous.

**Physical Examination**—The patient is emaciated and jaundiced, with coated tongue, no enlargement of lymph-nodes. Temperature is subnormal, pulse and respiration normal, lungs and heart negative. Abdomen shows constriction at costal margin, prominent wave present, no movable dullness, veins engorged about flanks. Liver is 3 cm. below costal margin in nipple line. The spleen is negative. The urine is deep brown, floccular sediment, acid, no albumin or sugar.

On the day before death an exploratory laparotomy by Dr. Hutchinson was followed by the escape of 6 or 8 pints of clear yellow fluid. The gall-bladder found to be distended but not inflamed and free from stones. There were four or five hard lumps about the common duct which on incision seemed to be involved glands. Over the dome of the liver nodules were found. The head of the pancreas and pylorus were free. There were a few adhesions between the gall bladder and intestines. The patient died shortly after this and the necropsy was performed through the operative incision by Dr. E. B. Krumbhaar, twenty hours after death. His notes are abstracted as follows.

**Necropsy**—The abdomen contained 500 cc. of thick bloody fluid. The general description of the abdominal cavity corresponds to that found at operation. The liver weighs 1,530 gm., measures 25 by 19 by 9 cm. It is of normal shape and consistence and an olive green color in which bright streaks of reddish purple are visible. The capsule is not thickened, but occasionally light yellow circumscribed spots are visible over the surface. These areas have a definite outline, are sometimes irregularly circular, sometimes elliptical and sometimes very irregular. They feel somewhat softer than the surrounding tissue and are very slightly depressed. The cut surface of the liver shows fairly distinct lobular markings with yellowish-green peripheral zones and olive green central zones. The areas described on the surface are found to extend several millimeters into the liver tissue. On the surface there are also found bright reddish purple streaks which in the cut section are seen to extend diagonally deep into the liver tissue like veins in marble. At the junction of the two lobes a striking picture is presented of dilated bile stained veins surrounded by yellowish margins which quite replace the normal liver tissue. These masses in places are quite hard and firm and in other places comparatively soft. They gradually infiltrate the liver structure and occasionally greenish islands can be seen isolated in the yellowish mass. On dissecting out the common duct it is found to be patulous, though at one place it shows a ragged wall connecting it with the green stained connective tissue mass. The cystic duct is patulous and bile readily flows from the gall bladder to the duodenum. The hepatic duct, however, shortly before its junction with the cystic duct is found to be invaded by the yellowish growth before described, so that it is impossible to pass a probe any distance into the liver. The lymph-nodes at the hilum of the liver are enlarged and made up of resistant elastic yellowish tissue.

The description of the various organs corresponds to the gross anatomical diagnosis. Primary tumor of liver causing obstruction of hepatic duct and hepatic veins, general icterus and emaciation, multiple infarcts (?) of liver, metastases of tumor to pleura and mesentery and retroperitoneal lymph-nodes, congestion, edema and partial atelectasis of right lung and intestinal peritoneum, cloudy swelling of kidneys, chronic cholecystitis, healed tuberculosis of lungs.

Microscopically, sections from the liver taken where the tumor involvement is not especially marked show an outer capsule of normal thickness, and a perilobular capsule which is distinctly overgrown. The tissue is loosely arranged and with the Weigert stain shows a moderately rich elastica. The blood-vessels show little change except for the presence of well-marked venous stasis and an occasional venous thrombus. None of the thrombi show the presence of tumor elements. The bile-ducts are definitely increased in number and occasionally show clubbing at their ends or other irregularities to suggest beginning atypical proliferation. The cells of the parenchyma show advanced cloudy swelling throughout and in addition those placed centrally in the lobules are distinctly atrophic, more markedly degenerate and in places distinctly necrotic. The central vein is congested, and with the Mallory connective tissue stain perivenous fibrosis running out between the necrotic cells is very well marked.

The sections taken from tumor proper show small areas where the picture is the same as that described above, but the greater part of these sections show dense connective tissue masses containing a few smooth muscle bands and richly infiltrated with an epithelial overgrowth showing itself in the form of small acini which sometimes are lined by columnar cells like those of the bile-ducts, sometimes by larger cuboidal cells with relatively large vesicular nuclei and occasionally seen as irregular masses of irregularly hexagonal cells showing no lumen whatever. In some fields masses of this sort appear as terminal bulbs attached to the smaller tubular acini. Mitotic figures are fairly numerous. The lumina of many of the acini are filled with a finely granular faintly basophilic material, evidently mucin. The entire mass, both epithelium and connective tissue, appears to substitute itself for liver tissue, the parenchymatous cells undergoing more or less marked necrosis in the neighborhood of the advancing growth. Areas are found with changes intermediate between the moderate bile duct proliferation of the first section and the distinctly malignant growth of the second section and from this point of view it would appear that the growth is from the bile-ducts. In other places there appears to be direct transformation from parenchymatous cells into cancer cells, but this appearance might easily be the result of the invasion of the tumor mass. Venous thrombosis is present in these sections but no cancer-cells are observed in the thrombi. Granules of bile-pigment are observed in the liver lobules in all sections but no evidence of it is seen in the tumor.

Sections from other viscera were examined and the microscopic diagnosis in full reads: Brown atrophy of myocardium and fibrosis of the mural endocardium, congestion and caseous tuberculosis of lungs, primary adenocarcinoma of liver with metastases to pleura, peritoneum, mesentery, retroperitoneum, pancreas, adrenal and lymph-nodes, moderate perilobular cirrhosis, cloudy swelling, biliary pigmentation and passive congestion of liver, cloudy swelling of kidney.

To summarize, this case is one of primary adenocarcinoma of the liver probably originating in the finer bile-ducts, in a man aged 40. Clinically the course was short, there was a history of alcoholism, icterus, ascites, and edema of the legs were present. Pathologically, the features were the presence of the primary growth associated with cirrhosis and fairly wide-spread metastases.

CASE 6—*History*—M. N., Chinaman, aged 56, was a patient in the Pennsylvania Hospital, in the service of Dr. Newlin (No. 1,137). The autopsy was per-

formed by Dr Longcope, who furnished me with the specimens and records. An abstract of the clinical history follows.

The chief complaint is diarrhea and fulness in the abdomen. Temperature, 97, pulse, 92, respiration, 24, on admission. The patient has never been sick more than a day or two at a time until the present illness, has lost weight gradually for ten years, smokes opium.

*Present Illness*—The patient has been sick two months, the abdomen has been swollen three weeks. The patient has had pain in hypochondrium two weeks. His appetite is poor.

*Physical Examination*—The patient is emaciated, jaundiced, marked arcus senilis, tongue dry, coated. Abdomen distended and contains fluid. Liver and spleen not palpable. Slight edema of feet and ankles.

Urine Clear, deep amber, acid, 1.031, no sugar, trace of albumin, contains bile, cylindroids.

Blood Hemoglobin, 75 per cent, leukocytes 11,200, red blood cells, 4,340,000. Stools show occult blood.

The patient became delirious before he died.

*Necropsy*—The abstract of the notes is as follows. Gall-bladder contains more than 100 cc of dark greenish-brown bile, its wall is thin and the mucous membrane is grayish in color. Cystic duct is patulous. Hepatic duct is slightly dilated as it enters the liver and its course cannot be followed very far. Both ducts contain a small amount of soft reddish gray material.

Mesenteric veins are blocked by the same material.

Liver weighs 1,850 gm, measures 30 by 16 by 9 cm, it is dark grayish yellow in color mottled by yellowish white to dark green elevated areas measuring from a pin head to 1 cm in diameter. Elevations are numerous and very irregular in shape and distribution, the yellowish white elevations are more numerous in the left lobe and the greenish ones in the right. These elevations are glistening but the tissue separating them is opaque. In the right lobe, either anteriorly or posteriorly, the greenish gray and brownish-red elevations predominate except around a cicatricial band of white, hard tissue 12 cm in length, which starts at the junction of the lower border of both lobes and goes upward and backward, this shows many yellowish-white elevations. On section the liver is very flabby, and green to yellow in color, lobulation is obscured, but at the upper portion of the dome a few greenish-yellow lobules can be seen surrounded by dark brown interlobular tissue. The liver substance is almost entirely taken up by irregularly rounded, soft, dark yellowish-white nodules measuring from 1 to 3 mm. These nodules are more numerous at and around the hilum, and they are in places small, light yellow and in others larger and almost confluent, whitish yellow with many small white dots. On pressure one can squeeze out dark brown material mixed with light yellow and dark red substance. The hepatic veins and artery are found free from any suppuration, but the portal vein is blocked for a distance of about 10 cm. from its free course, with soft red material striped with yellow. As the vein enters the liver this material is so adherent to the wall that it seems as if it were growing from it. From this point on to the finest visible branch the vein is blocked with the same material.

The remaining organs correspond in appearance with the gross anatomical diagnosis. Carcinoma arising in liver, with extension into portal vein, thrombosis of pulmonary artery, ascites, chronic perisplenitis, slight splenic tumor, follicular cholecystitis, dilatation of common and cystic bile ducts and gall-bladder, congestion of lungs, arteriosclerosis.

Microscopically, several slides were studied and the report is a composite one. The outer capsule is considerably thickened and the perilobular connective tissue markedly increased. The interacinous bile ducts are moderately increased in number but not so much so as would be expected for the grade of cirrhosis. The veins are much congested and in many cases filled with neoplastic thrombi. The cells of the parenchyma show advanced cloudy swelling and central atrophy, but the most striking change in them is a wide spread necrosis which appears in both

peripheral and central positions and is too extensive to be looked upon as the usual expression of focal necrosis. The central veins are markedly congested but show little fibrosis. Throughout the lobules but most noticeable in their periphery are enormous numbers of amorphous dark green pigment masses, very clearly defining the intralobular bile capillaries in the unstained specimens. The tumor masses are distributed irregularly and profusely throughout the sections, often more or less limited to the perilobular structures, again penetrating clearly within the acini. The cells are of irregular outline and variable size but generally somewhat larger than the liver cells. They are arranged in clumps which are quite free from connective tissue (with Mallory stain) and show no attempt at gland formation. The protoplasm is rich and vacuolated as if by fat globules. The nuclei are large, oval, vesicular and show frequent mitoses. Here and there large protoplasmic masses are found containing multiple nuclei. In masses quite free from veins, fairly large areas of hemorrhage are found. No transitional connection between liver parenchyma and new growth can be demonstrated. The large number of neoplastic thrombi in the perilobular veins is a striking feature. Sometimes the thrombi appear to dilate the veins. In other cases the veins are not dilated very markedly but are completely occluded by the tumor cells. A few of these neoplastic masses are in perivascular situations and would seem to be lymph spaces rather than veins. In some of the larger veins much of the elastica has been destroyed by the tumor growth.

Microscopical examination of the other viscera was made and no metastases noted. Microscopical diagnosis: Carcinoma solidum of liver with extension into portal vein, passive congestion, necrosis, biliary pigmentation of liver, congestion and follicular hyperplasia of spleen, chronic diffuse nephritis.

To summarize, this is a case of primary carcinoma of liver of solid form, occurring in a Chinaman 56 years of age. Clinically there is a history of opium-smoking, short duration of illness, emaciation, jaundice, ascites and slight edema of feet and ankles. Pathologically there is the tumor with portal vein thrombosis, no metastasis, slight splenic tumor, and the thrombosis of the pulmonary artery which appears not to have been neoplastic. Hemorrhage is noted in tumor areas but is very slight. It is significant, however, in that in one case at least, that of Ewing,<sup>12</sup> it was severe enough to have been the cause of death.

**CASE 7—History**—L. F., an Italian, aged 34, was a patient in the Pennsylvania Hospital (1,152), on the service of Dr. Tyson. The records and specimens were furnished me by Dr. Longcope. An abstract of the history follows. Chief complaint, jaundice, abdominal pain and fulness. The family history is negative. The patient is a steady drinker, smokes to excess, good appetite, bowels regular.

**Physical Examination**—Well nourished, skin quite yellow, skin of flanks scarred in linear striæ as if by distention. No marked prominence of abdominal veins. Tongue coated, teeth good. Thorax, lungs and heart negative. Abdomen tense, dome-like tympanitis in upper part, movable dullness in flanks. Spleen not palpable, no tension nor rigidity. Liver, sixth rib to costal margin.

Urine cloudy, brown, 1018, acid, faint trace of albumin, much bile, few hyaline and granular casts.

Blood: hemoglobin 87 per cent, leukocytes, 11,300, of which 88 per cent were polymorphonuclears, 3 per cent small, and 4 per cent large lymphocytes, 4 per cent eosinophils, 1 per cent basophils.

Jaundice increased, as did the emaciation. Patient developed constipation and anorexia.

Cytolytic examination of the fluid in the abdominal cavity showed many large mononuclear cells

*Necropsy*—This was performed by Dr Longcope nine hours after death, whose notes are abstracted as follows. Liver measures 27 by 19 by 10 cm, weighs 1,800 gm. It is of a deep green color and presents a rough, irregular, hobnailed appearance. In several places on the surface the hobnails stand out, being bright green or pale yellow in color. These yellow nodules are scattered and not numerous. On section the cut surface shows a coarse, bright green, irregular lobulation. Here and there the same grayish or pale yellow lobules take the place of the green lobules. Over one area about 5 cm in diameter there are several raised, very soft bright yellow rounded nodules showing some centrally placed radiating red striæ. When cut they show soft pus-like centers in an irregular cavity. There are various openings in the cavity which can be traced directly into the main hepatic duct and when the puriform material is removed the wall of the cavity is found to be lined with a well-defined white membrane. At some distance from the central mass there are small soft raised yellow masses which connect directly with the main cavity. When the portal vein is opened it is found to be filled with a tumor-like mass about 5 cm across. This is situated at a point where the vein divides and completely occludes and distends it. The mass is soft, friable, orange-yellow streaked with red and firmly adherent to the wall of the vein. It extends for some distance down the branch running to the left lobe where it becomes soft and of the same nature as the tumors filling the bile ducts and cavity in the liver. The same condition is seen in the main portal vein, where the tumor gradually tapers down to a red clot which partially fills the vessel and does not extend as far as the entrance of the splenic and superior mesenteric veins. No connection can be found between the main branches of the portal vein and the bile ducts or the large softened areas in the liver.

The other organs correspond in appearance with the gross anatomical diagnoses. Atrophic cirrhosis of liver, tumor arising at hilum and involving and occluding the portal vein and hepatic duct and its branches, splenic tumor, ascites (2,600 cc), subserous hemorrhages of stomach, intestines and pericardium, hemorrhage from mucous membrane of colon, general icterus, acute seropurulent pericarditis, congestion and partial atelectasis of lungs, congestion and jaundice of kidneys with chronic diffuse nephritis, chronic interstitial pancreatitis with fat necrosis.

Microscopically, several specimens of liver were examined, the notes making a composite picture. The outer capsule is fibrosed and the perilobular fibrous tissue is overgrown and richly infiltrated with lymphocytes and a few leukocytes. The blood-vessels are congested and several of the veins show neoplastic thrombi. The bile ducts are enormously increased in number and appear both in interlobular and intralobular position. When in intralobular positions they are accompanied by an overgrown connective tissue mass, quite free from elastica. These ducts often show terminal clubbing, the cells in the clubbed area being identical in morphology with liver cells but not containing bile pigment. The liver lobules are irregular in outline and often much diminished in size. The cells of the parenchyma show well marked cloudy swelling and in the center of the lobule are atrophic. The finer bile canaliculi are choked with amorphous dark green bile-pigment throughout. Many extensive areas of necrosed liver cells are observed. The tumor masses are scattered irregularly over the field and usually show as fairly well defined areas somewhat larger than a liver lobule made up of large irregular cells about the size of a liver cell and with identical tinctorial characters. The protoplasm in many shows fine vacuoles similar to the fat vacuoles of liver cells. Mitotic figures are not frequent and nuclear fragmentation is common. These areas show central necrosis and often are infiltrated rather richly with polymorphonuclear leukocytes. Extension into the veins is fairly common, in most cases the vessels being completely occluded and slightly distended by the solid tumor masses. In no place where the tumor is definitely malignant can any attempt at gland formation be made out. Invasion of the sheath of one or

the smaller nerve-trunks is observed but is not extensive. This is a feature that has been described as being prominent in a case reported by Conti<sup>4</sup>. No connection can be observed at any point between liver tissue and tumor or the proliferated bile ducts and tumor. The growth in the portal vein is like the main tumor mass. The cells are attached to the wall of the vein, which latter is partly distended.

Other organs were examined microscopically, the diagnosis including Carcinoma solidum, atrophic cirrhosis, necrosis, neoplastic thrombosis of liver, hemorrhages in pericardium, duodenum and gall-bladder, chronic interstitial pancreatitis with fat necrosis.

To summarize, this case is one occurring in a man 34 years of age. Clinically he has a history of alcoholism, shows emaciation, icterus and ascites. Pathologically the liver tumor appeared as if it might have started from the larger bile-ducts, but histologically it is a cancer whose cells so closely resemble those of the liver that they must be responsible for its origin. There is cirrhosis and venous thrombosis but no evidence of metastases outside the liver.

**CASE 8—History**—D. I., a Russian boy, aged 8, was a patient in the Pennsylvania Hospital (1,295), on the service of Dr. Mitchell. The specimens and records were furnished me by Dr. Longcope. A brief abstract of the clinical history follows. Chief complaint, abdominal pain. Patient's mother says the boy has been sick about a week but was taken acutely ill about two nights before admission with severe abdominal pain accompanied by vomiting and pain on the right side. He had also been having a cough with yellowish thick expectoration, headache, pain all over, fever for two days, loose stools, no chills, no convulsions.

**Physical Examination**—Fairly well-nourished boy, tongue heavily coated. Lymph-nodes not palpable. Lungs show a few scattered bronchial râles. Heart, rapid, pulse weak, fairly loud systolic murmur heard best at apex. Abdomen distinctly tender in lower right quadrant, slightly rigid, no mass palpable. Extremities are negative. Examination of blood in receiving ward shows 35,000 leukocytes.

Operation was performed on admission after which the patient grew steadily weaker and died. Urine, after ether, acid, 1.010, trace of albumin, many granular and hyaline casts, epithelial cells, leukocytes.

**Necropsy**—This was limited to the abdomen and was performed by Dr. Draper, whose notes are abstracted as follows. Liver, about normal in size, measures 18 by 12 by 6 cm., is filled with nodular masses of varying sizes, the largest being half the size of a lemon. The capsule of the organ is smooth and glistening. Surface only slightly irregular. The color of the organ is purplish brown mottled with pale yellowish areas where the large masses shine through, these represent the sections of tumor masses. The liver tissue itself exists as narrow strand-like masses between the tumors. It is pale purple in color mottled with yellow. The markings are not recognizable. The tumors themselves are yellow, sharply defined and firmer than the liver tissue. They have a tendency to bulge above the cut surface.

The other viscera show congestion and there is splenic tumor and follicular hyperplasia. The gross diagnosis of the liver was multiple adenoma.

Microscopically several sections of the liver were studied. The outer capsule of the liver is moderately overgrown and the perilobular connective tissue also shows well-marked fibrosis. The blood-vessels are moderately congested and there is extensive neoplastic thrombosis of the perilobular veins. Increase in the number of bile ducts between the acini is noted but is not very marked. The peripheral cells of the lobules show marked cloudy swelling, many of the central cells show well marked vacuolation from the presence of fat. The nuclear changes



in the parenchyma are notable, there being enlargement and increase in the number of nucleoli in the peripheral cells, and diminution in size, fading and peripheral grouping of the chromatin in many of the central cells. The central vein is moderately congested. The larger tumor masses are surrounded by fairly dense connective tissue masses free from smooth muscle and very poorly supplied with elastica. The masses are solid peripherally and necrotic centrally, but show no areas of hemorrhage. The cells are large and irregular in outline, grouped in masses without fibrillar tissue. The protoplasm is often the seat of very well-marked vacuolation and a few multinucleated large protoplasmic masses are found. Mitotic figures are fairly numerous. The mass is not limited by its fibrous tissue capsule but pushes out in all directions, through veins and lymph-spaces, through perilobular and intralobular tissues. In the last situation fine cords of tumor cells are found in continuity with liver chains but no transitional connection is seen. The extension in the veins is well demonstrated with the Mallory connective tissue stain and by the Weigert elastica stain. There are also numerous solid finger-like tumor masses running through the interlobular connective tissues in well defined spaces free from muscle and blood which evidently are lymph-spaces.

Slides from other tissues were examined and the histological diagnosis includes Carcinoma solidum, fatty degeneration, passive congestion, carcinomatous thrombosis of liver, congestion and cloudy swelling of kidneys, general lymphatic hyperplasia, slight post mortem degeneration of adrenals.

To summarize, this case is one of primary carcinoma of the liver in a boy 8 years of age. Clinically there were indefinite gastro-intestinal symptoms, pain and tenderness over the liver, leukocytosis, absence of icterus and ascites. Pathologically the tumor is a carcinoma solidum, grossly of the type often called "multiple adenoma" associated with neoplastic thrombosis of veins but without metastases other than local, unless there were metastases in the unexamined lungs.

**CASE 9—History**—C. B., an Italian man, aged 40 years, was a patient in the Pennsylvania Hospital (304). The specimens and records were furnished me by Dr. Longcope. The patient was admitted in October, 1902, and his clinical history is abstracted as follows. Patient had severe attacks of chills and fever for eight days in the previous July and again in August two weeks later, when he became intensely jaundiced which continued up to the time of admission. During the past four weeks patient has had a dull aching in the hepatic region about the costal margin, no vomiting, stools clay colored.

**Examination**—On admission patient was intensely jaundiced. Liver extended 5 or 6 fingers' breadths below the costal margin, felt hard, smooth and regular. Gall-bladder was not palpable, the entire hepatic area vague in outline and patient had a constant dragging pain, relieved by lying on the right side.

Pain in hepatic area increased during the patient's stay in hospital. Gall-bladder was drained September 29, but patient died October 3.

**Necropsy**—This was performed by Dr. Flexner, four hours after death. His notes at the time are abstracted as follows. Liver weighs 2,400 gm., measures 21 by 21 by 13 cm. It is fairly large, and of exceedingly firm consistence, it is of a brilliant green color, mottled finely with irregular yellow and black markings. The surface is slightly irregular but not lobulated and smooth with the exception of a few fresh adhesions to the gall bladder region. Near the lower margin of the right lobe there is a yellow depressed scar, irregular, but in general about 3 by 2 cm. in diameter. It lies about 1 cm. below the general surface and the margins are composed of liver tissue, rounded and contracted down to it. Six more such yellow depressed scars are found over the surface, varying from 0.5 to 2 cm. in diameter.



The gall-bladder is distended and shows a quantity of reddish, semi-liquid blood clot. The common bile-duct shows a most marked distention, measuring 4 cm in diameter and 10 cm in length, about it are several flattened soft large lymph-nodes, there is no constriction of the duct whatever. The distention of the duct extends into the liver and when the clots are removed a grumous fluid mixed with pus pours from the duct within the liver when the organ is pressed.

On section through the liver the surface has the same mottled grass-green and yellow aspect as the capsule. Lobular markings are obliterated. Near the hilum the bile-ducts are enormously distended and filled with dark grumous material and pus. In the middle of the right lobe a yellow irregular, opaque area is cut through similar to those on the surface, and in the left lobe another such area is found. Small yellow opaque discrete extensions radiate toward the surface of the liver, but toward the hilum these areas are covered with soft reddish-green necrotic mass. Connective tissue is much increased in the hilum and extends into the vessels and into the lobules of the organ.

Autopsy showed a small amount of fluid in the abdominal cavity and the various viscera corresponded in description with the gross anatomical diagnosis. Cirrhosis of liver with multiple adenomata, acute hemorrhagic cholangitis, distention of common bile-duct but no cholecystitis, acute bronchopneumonia, chronic interstitial splenitis, chronic diffuse nephritis, general icterus.

The microscopical picture offered is a composite of several slides. The outer capsule is of about normal thickness and the perilobular fibrous tissue is considerably overgrown. The blood-vessels show well-marked congestion and several are distended by neoplastic thrombi, which will be described later. The interlobular bile ducts are markedly increased in number, irregular in outline, often appearing as solid cords and with connective tissue appear to be replacing liver parenchyma. The liver cells show advanced cloudy swelling and toward the central vein distinct atrophy. The vein is moderately congested. All the sections show small necrotic areas, less extensive than a lobule, irregularly placed, sharply outlined and containing compound granule cells whose nuclei have disappeared, evidently necrotic liver-cells. Hemosiderin pigmentation and bile pigmentation of the liver cells are observed, the former especially in the neighborhood of the necrotic areas. In one slide an area 5 mm in diameter is made up almost entirely of irregularly arranged fibrous tissue, rich in fibrillæ and poor in nuclei. An interesting feature of this mass is that, with the Weigert elastica stain, it is almost black. About its margin the number of small bile-ducts is very great. Several fairly large bile-ducts are included in the sections and these are filled with blood and the blood apparently has extended into the smaller ducts, for in the immediate neighborhood several small ducts whose morphology is typically that of the "proliferated" ducts there is also much blood. The tumor itself is of the solid type, showing as masses of epithelial cells irregularly grouped together in fairly large clumps surrounded by a connective tissue mass but distinctly infiltrating it. The cells vary from columnar and cuboidal cells to large irregular cells, and in some places large multinucleated protoplasmic masses are found. The cell nuclei are large, vesicular and generally oval in shape, and numerous mitoses are found. No connection with preexisting liver tissue is found. Several large veins are included in the sections. With the special stains they show a small amount of smooth muscle and several bands of elastica. They are almost filled with a thrombotic mass, which toward the vessel wall is solidly made up of cells like those found in the tumor masses, but which centrally becomes more and more mixed with clotted blood. The lumina are small but not completely occluded in any case. In spite of this extensive thrombosis no metastases were observed other than those seen in the liver itself.

Sections of other tissues were studied and the histologic diagnoses are: Chronic interstitial splenitis, chronic diffuse nephritis, carcinoma solidum, cirrhosis and focal necrosis of liver.

To summarize, this case appeared in a man, aged 40 years. Clinically the case was of short duration, showed icterus, slight ascites and pain

in the liver region. Pathologically the tumor was grossly of the type often called "multiple adenoma," showed local metastases, neoplastic thrombosis, cirrhosis, bile duct proliferation and focal necrosis.

In reference to the preceding two cases it must be said that the term multiple adenoma has a significance in connection with diseases of the liver that it does not have in other connections. Von Griesinger,<sup>13</sup> Rindfleisch<sup>14</sup> and Eberth<sup>15</sup> took the view that it is a distinct pathologic entity. Among the first to combat this view was Gilbert,<sup>16</sup> and of the more recent writers taking this position are Cloin,<sup>17</sup> Muir<sup>18</sup> and Alezais and Corsy.<sup>19</sup> Masterly, however, is the summing up by Marckwald,<sup>20</sup> who states in no uncertain terms that this tumor is a cancer. Further, he states that the more or less definite fibrous capsules around the tumor masses are made

TABLE OF NINE CASES OF PRIMARY

Case, Age and Sex	Nature of Cancer	Origin	Cirrhosis	Changes in the Liver	
				Cells	Bile Ducts
1—40—F	Adenocarcinoma of the massive form	Smaller bile ducts	Present	Cuboidal and low columnar, mitoses common	Proliferated, interacinous
2—49—M	Adenocarcinoma of the nodular form	Smaller bile ducts	Very slight	Low columnar, mitoses infrequent	Proliferated, interacinous
3—11—F	Adenocarcinoma of the nodular form	Smaller bile-ducts	Present	Low columnar, no mitoses, necrosis	Proliferated, interacinous
4—53—M	Adenocarcinoma of nodular form, shows solid masses also, histologically	Smaller bile ducts	Marked	Low columnar, mitoses	Proliferated, interacinous
5—52—M	Adenocarcinoma of the nodular form	Smaller bile ducts	Moderate	Low columnar, often showing transition to hepatic cell forms, numerous mitoses, necrosis	Proliferated, interacinous
6—56—M	Carcinoma solidum of nodular form	Liver cells	Moderate	Liver cell type, frequent mitoses, necrosis	Slightly proliferated, interacinous
7—34—M	Carcinoma solidum of nodular form	Liver cells	Marked	Liver cell type, infrequent mitoses, necrosis	Markedly proliferated, interacinous and intra acinous
8—8—M	Carcinoma solidum of nodular form, "multiple adenoma"	Liver cells	Moderate	Liver cell type, numerous mitoses	Slightly proliferated, interacinous
9—40—M	Carcinoma solidum of nodular form, "multiple adenoma"	Liver cells	Moderate	Liver cell type, numerous mitoses, focal necrosis	Markedly proliferated, interacinous

up for the most part of newly formed connective tissue, the course is relatively short and the condition may be the chief cause of death. Ribbert<sup>21</sup> offers a new class of somewhat similar tumors which he calls malignant adenomata of the liver, tumors originating in liver-cells, extending through the organ by continuity in the vessels or through metastasis by

13 Von Griesinger Arch f Heilk, 1864, v, 385

14 Rindfleisch Arch f Heilk, 1864, v, 395

15 Eberth Virchows Arch f path Anat, 1868, xlii, 1

16 Dérignac et Gilbert Gaz méd de Paris, 1884, h, 28

17 Cloin Prag méd Wehnschr, 1901, xxi, 261

18 Muir Jour path and Bacteriol, 1903, vii, 287

19 Alezais and Corsy Marseille Méd, 1903, xiv, 353

20 Marckwald Virchows Arch f path Anat, 1896, cxlv, 29

21 Ribbert Deutsch med Wehnschr, 1902, xxx, 1607

way of the portal vein and showing the power of bile-production This is a tumor with functional powers simulating the function of the cells from which it originated

Such classifications, however, can only serve to confuse a subject already complex and neither the malignant adenoma nor the multiple adenoma differ from the ordinary forms of liver cancers sufficiently to justify the separate classification This point of view is taken by the majority of modern writers and my study of the subject leads me to accept it without further qualification For this reason Cases 8 and 9 have been included in this series

The accompanying table is modelled after Eggel's table and slightly modified The cases are not sufficient in number to permit far-reaching

## CARCINOMA OF THE LIVER

Blood-Vessels	Extra-Hepatic Metastases	Duration	Etiology	Jaundice	Ascites	Edema	Splenic Tumor
Slight tumor thrombosis	Right adenal and subhepatic lymph-nodes	3 months	Coffee	Present	None	None	Present
Slight tumor thrombosis	Lungs, pleura, pancreas, left kidney, retroperitoneal lymph-nodes	1 week (?)	Lead	None	Moderate	(?)	None
No thrombosis	None	11 months		Present	Marked	Marked (anasarca)	Marked
Moderate tumor thrombosis	Lungs, mediastinal, retroperitoneal and mesenteric lymph-nodes	2 months	Tobacco enough to produce leukoplakia	Slight	Present	Present	Present
Blood thrombosis not neoplastic	Pancreas, adrenal, peritoneum mesentery, pleura, lymph-nodes	4 months	Alcohol	Present	Present	Present	(?)
Tumor thrombosis in portal vein	None	2 months	Opium (?)	Present	Present	Present	Slight
Tumor thrombosis	None	(?)	Alcohol	Present	Present	None	Present
Extensive tumor thrombosis	None (?)	1 week		None	None	None	Present
Tumor thrombosis	None	4 months	(?)	Marked	Slight	None	None

conclusions to be drawn, but a brief analysis seems advisable The age of the patient is altogether in late middle life with the exception of two cases which have appeared in rather early life Philipp<sup>22</sup> states that cancers of the digestive tract, including liver and pancreas, contribute 46 per cent of all cancers occurring before the age of 15 years In Eggel's statistics there were but five cases occurring before 20 years of age Cade,<sup>23</sup> Petrone,<sup>24</sup> Risicato,<sup>25</sup> Majumdar,<sup>26</sup> Mattiolo,<sup>27</sup> Wegelin<sup>28</sup>

22 Philipp Ztschr f Krebsforsch, 1907, v, 236

23 Cade Lyon Méd, 1906, cvii, 1053

24 Petrone Pédiatrie prat, 1907, v, 109

25 Risicato Pediatria, Naples, 1905, series 2, iii, 772

26 Majumdar Indian Med Gaz, 1905, xl, 306

27 Mattiolo Gaz d osp, 1905, xxvi, 732

28 Wegelin Virchows Arch f path Anat, etc, 1905, clxxix, 95

have reported cases in early life and it would appear that, as the study of carcinoma in early life is prosecuted further, cancers of the liver will be found to be of somewhat greater frequency than is supposed at the present time

Little need be said as to sex, for the predominance of this affection in the male sex is well shown in the table (seven out of nine cases) and similar proportions are recorded by all modern writers

The microscopic character of the tumor is found to be adenomatous in five cases and simple or solid in four cases. Various writers disagree as to which form predominates and Eggel's statistics show the reversed proportion, sixty-two cases of carcinoma solidum and fifty-five cases of carcinoma adenomatosum. That statistics might be very much prejudiced is well shown by the fact that all my own cases were of the type of adenocarcinoma and of the five cases furnished me by Dr Longcope four were of the solid type. Grossly eight of the nine cases are nodular cancers, the other being a massive type. The predominance of the nodular form is more marked in my series than in series of greater number, and all statistics point to this as the most frequent form. The diffuse cancer is one which resembles a hypertrophic cirrhosis so closely in the gross that it is often impossible to make the diagnosis without the microscope.<sup>29</sup> It is a rather rare form, constituting about 12.4 per cent of the reported cases.

The cells from which the tumor originated have been put in the table with some mental reservation, for, although some authors have reported seeing transformations directly from liver-cells into cancer, and from bile-ducts into cancer a detailed study of these nine cases fails to convince me that such transformation can be demonstrated. A very close resemblance can be seen between the tumor-cells in some of the cases and liver cells as is true also of the duct epithelium and the tumor-cells, but inasmuch as transformation of the morphology of the cells can be seen very distinctly in the small bile-ducts in cirrhosis of the liver and in regeneration after acute processes such as acute yellow atrophy,<sup>30</sup> it would seem reasonable to suppose that such transformation can occur in neoplastic processes thus interfering with deductions drawn on a purely morphological basis.

The question of the association of cirrhosis and cancer of the liver is a living one and is the basis for a wide range of discussion and opinion. It will be noticed that all nine cases show more or less marked cirrhosis. Of Eggel's cases cirrhosis was mentioned clinically in connection with eighty-two and found present at autopsy in seventy, the proportion being about the same in the two microscopic forms.

29 Herzheimer *Centralbl f allg Path u path Anat*, 1906, *xvii*, 724

30 Mac Callum *Johns Hopkins Hosp Rep*, 1902, *v*, 375 Barbacci *Beitr z path Anat u z allg Path*, 1901, *xxx*, 49

Two essential views are held as to this relationship, the first being that the two are present in the livers simply as the result of coincidence, Frohmann<sup>31</sup> taking this stand. It is true that relatively few cases of cirrhosis of the liver show cancer, yet they show cancer-like changes in the increased number of ducts and the isolated islands of irregularly arranged liver-cells, sometimes, in my experience, to such a degree as to render the final diagnosis very difficult. Rolleston<sup>32</sup> goes so far as to say that mistakes of this sort have been made in many cases. In spite of this, the very marked frequency of their concurrence, and the fact that secondary cancers are not very commonly associated would lead me to reject such a view.

By those who believe that the two conditions are more or less inter-related, several views are expressed. Gilbert and Claude<sup>33</sup> with some others assert that the cancer is the primary process and produces the cirrhosis, probably by producing stagnation of the bile or by the direct action on the connective tissue of the toxic products of the cancer itself. Bile-stagnation, however, although common, does not appear in all cases and, as has been mentioned before, the occurrence of secondary cancers frequently is unassociated with cirrhosis. The weight of opinion is decidedly against this view.

Many claim that the cirrhosis precedes the cancer and is etiologically at the basis of the malignant growth. To appreciate this view it is necessary to accept the view that cirrhosis is secondary in itself to some injury to liver substance and that the fibrosis occurs as a replacement process. Clinical and experimental observation point this way so strongly that the assumption seems fully warranted. Following out this idea leads us far afield into the study of liver regeneration, a study probably first undertaken from the experimental side by von Podwyssowski<sup>34</sup>. He found that in different animals the removal of fairly large pieces of liver were followed by proliferative changes in the connective tissue and epithelium, the latter in some animals being more marked in the finer bile ducts and in other animals in the liver cells. Ponfick<sup>35</sup> reached somewhat similar conclusions. Of the more recent experiments those of Jaeger,<sup>36</sup> studying aspergillus mycosis in deer, led him to express the same view. Many workers in human pathology are of the opinion that bile-duct proliferation or multiplication of the hepatic cells occurs as the sole means of regeneration but personal observation of several hundred degenerate livers, including many cases of cirrhosis, leads me to accept the view that both liver cells and bile-ducts play a part in liver regeneration and that

31 Frohmann Inaug Diss, Königsberg, 1892

32 Rolleston Tr Path Soc, London, 1901, II, 203

33 Gilbert and Claude Arch gén de méd, 1895, cxxv, 513

34 Podwyssowski Beitr z path Anat u z allg Path, 1886, I, 259

35 Ponfick Virchows Arch f path Anat, 1895, cxxviii, 51

36 Jaeger Virchows Arch f path Anat, 1909, cxvii, 45

the connective tissue overgrowth is essentially a substitution process. This view is supported by Mac Callum<sup>37</sup> and others who have made extensive studies in this field. The multiplication of liver-cells according to my own observation is almost certainly by amitotic division, but I am not prepared to state the mode of division into the multiplication of the bile-duct epithelium.

That diffuse or more or less localized destruction of the liver parenchyma may lead to very marked proliferation of both interstitial and parenchymatous elements has been referred to earlier. In order to apply this fact to cancer production it is necessary to call on Orth's view, expressed in his "Lehrbuch," that the epithelial proliferation overshoots the mark and produces malignant change. That necrosis or other degenerative change might have played a part is suggested, but not proved by any means, by the fact that in my series four cases showed it extensively and that in Case 9 a focalized scar was found, probably the result of an earlier focalized lesion.

The frequent proliferation of bile-ducts is called on to support the view that cirrhosis is primary, but I cannot accept this because I find it present equally in the cases of liver-cell cancer as well as in the adenocarcinomata, and in no case was I able to find connection between the proliferated bile-ducts and the cancer. This phase of the subject will be referred to later.

Fraser<sup>38</sup> in this connection suggests the ingenious explanation that there is present in the first place a hypertrophy of the connective tissue which first is loose, later shrinks irregularly and causes on the one hand a destruction of parenchyma, on the other hand compensatory proliferation, particularly in the parts not shrunken or in such places as there is little resistance to overcome. The balance of proof certainly lies with Fraser, as this supposition is in marked contrast to the generally accepted ideas as to the pathogenesis of cirrhosis.

A third view as to the relation of cirrhosis and cancer is that a productive or organogenic irritant produces proliferation of connective tissue, bile-ducts and liver parenchyma. This view is ably supported by Jaeger<sup>36</sup> in his work on deers' livers. There are many considerations which force me to regard this view favorably and numerous writers take the same position but again we are carried too far afield to warrant discussion in this paper.

The presence of tumor thrombosis is of very great interest in explaining metastasis, ascites and splenic tumor. That metastasis is not more frequent in connection with thrombosis is probably due to the rapid

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37 Mac Callum, W. G. Regenerative Changes in Cirrhosis of the Liver, *Jour Am Med Assn*, 1904, xlii, 649.

38 Fraser. *Virchows Arch f path Anat*, 1901, clxi, 540.

growth of the cancer and in few of these cases was there necrosis in the thrombi, a feature which means little probability of embolism

Metastasis in the liver is a common feature, as can be readily explained by the rich blood-supply and the numerous lymph-vessels which course through the trabeculae. Extrahepatic metastases are most common in the lung, although my series of cases does not give very much information as to this point. This feature, however, is almost certainly due to the rich venous thrombosis which occurs in connection with so many of these tumors. In spite of this fact, fairly rich thrombosis is found in cases where no extrahepatic metastases are recorded whatever, and as has been stated above, this can be due to the rapid growth of the tumor and the fact that necrosis is very infrequent in the thrombi.

The duration of the disease is short in all cases, another point borne out by all the statisticians. Two of my patients give a history of having been ill but a week. Naturally this cannot be accepted as final because of the notable inaccuracies of histories, particularly in the class of patients seen in the hospitals from which these cases were taken. Nevertheless that liver cancers run a course more rapid than cancers of most other viscera is a well-supported fact and is explained probably by the fact that the toxic products of the cancer have unusually ready access to the circulation, as can be inferred from the frequent venous thromboses. Again, metabolic and digestive functions of the liver are of extreme importance and the fact that the tumor spreads rapidly through the liver by virtue of the intercommunicating blood and lymph-spaces would lead to very rapid interference with these functions.

As to the history of the use of drugs which would lead to cirrhosis I have included coffee and opium and tobacco, which although not generally accepted as causes of cirrhosis, most certainly play an important part in its production. This point being accepted, all our cases with the exception of the two children and the last case show a history which includes some etiologic factor in the production of cirrhosis. This point should be regarded with considerable interest in connection with the question as to whether cirrhosis or cancer is primary.

Jaundice was present in seven of my nine cases and Eggel found it in 61 per cent of his cases. The histologic character plays little part statistically in the presence or absence of jaundice although grossly the condition is less frequent in the massive form than in the nodular form. Jaundice can be explained in various ways, probably most easily by assuming that the intrahepatic masses act to obstruct the outflow of bile. In Case 1 there was little doubt at the time of the autopsy that involved lymph-nodes in the hilum of the liver produced pressure on the hepatic duct and it is easily conceivable that such pressure might be sufficient to play an important part in the production of the icterus. The same is true of Case 5. Furthermore, the cachexia incident to liver cancers as

well as to other forms of cancer may be of moment in that the production of a cachectic anemia may lead to consequent hematogenous jaundice. Metabolic disturbances may add to this and there can be little doubt that the toxic products of altered metabolism may produce the so-called toxic jaundice.

Ascites was present in seven of my cases but not in precisely the same group which showed icterus. Eggel found it in 58.5 per cent about equally divided between the massive and nodular forms and most frequent in the diffuse (hypertrophic cirrhotic) form. Curiously, it is more frequent in those cancers which show the liver-cell type histologically than in those of the gall-duct type. Although toxic factors and the presence of anemia may play some part in the production of ascites yet the most probable causes, I think, are the associated atrophic cirrhosis and the frequent venous thrombosis of neoplastic and other origin.

Edema of the lower extremities was present in four of my cases and probably in a fifth case. Eggel found it in 41 per cent of his cases. In the majority of cases the edema must be laid to the anemia and toxemia but in a few it can be accounted for by the pressure of metastases, particularly those invading the lymph-nodes of the hilum, on the vena cava. Neoplastic or other forms of thrombosis in the vena cava have been known to produce edema in cases of cancer of the liver.

Splenic tumor is an inconstant feature in the larger series of cases but in my series it is seen to occur in six cases. The diagnosis in these cases is made from the point of view of the gross morbid anatomist and whether or not the clinician could demonstrate the condition in all these cases is, I think, questionable. It may be that toxic factors play a considerable part in the splenic enlargement and there can be little doubt that the general abdominal stasis is of great etiologic importance.

#### SUMMARY

To summarize, it may be said from the studies presented in conjunction with the literature reviewed, that primary carcinoma of the liver occurs more frequently in men than in women, is seen most frequently in the fourth and fifth decades of life and very often is accompanied by a personal history in which some etiological factor of cirrhosis of the liver is found. Clinically vague gastro-intestinal symptoms like those of early atrophic cirrhosis are noted and are followed by more marked digestive disturbance, cachexia and frequently jaundice. Ascites, edema of the lower extremities, splenic tumor and more rarely fever present themselves in a variable number of cases. The course of the disease is rapid.

Pathologically the disease shows three gross anatomical forms, nodular, massive, diffuse, and two microscopical forms, carcinoma solidum and carcinoma adenomatosum. In the liver itself cirrhosis is an associated condition in almost all cases, tumor thrombosis of the intrahepatic blood-



vessels is common and intrahepatic metastases are frequent. Extrahepatic metastases are more common and more widely spread than usually is believed and their distribution, together with the frequent presence of tumor thrombosis of the intrahepatic blood-vessels, lead to the conclusion that the transmission of the condition to the other organs is largely through the blood vascular system. In my opinion cirrhosis of the liver, or the factors which commonly are believed to produce cirrhosis, play an important part in the etiology of primary carcinoma of the organ and the tumor may originate from either the essential hepatic cells or from the bile-duct epithelium. These tumors arising from the liver-cells are more likely to be of the solid form and those from the bile-ducts are more likely to be of the glandular form, but this is not an invariable rule.

1320 South Broad Street

## BOOK REVIEWS

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DISEASES OF THE HEART AND AORTA By Arthur D Hirschfelder, M D, Associate in Medicine, Johns Hopkins University With an Introductory Note by Lewellys F Barker, M D, Professor of Medicine, Johns Hopkins University Cloth Price, \$6 Pp 632, with 329 illustrations Philadelphia J B, Lippincott Company, 1910

It is almost as agreeable, and indeed quite as stimulating, to find an old subject presented in a new and suggestive manner as to chance upon a new subject itself, and the former, as a rule, is far more apt to be quickly and widely received. The tremendous strides which have recently been made in assisting us to understand the complicated mechanism of the cardiovascular apparatus, both in health and in disease, have developed a new and much broader point of view regarding heart disease. Until the publication of this book most of the contributions which have brought about this somewhat different attitude of mind had not been incorporated in the older text books on the heart or modern system articles, nor have they exerted their full influence on them. The great value of the present book is that the author treats the subject in a new way. The recent results of anatomical, physiological, pathological and clinical studies are combined in such a manner that the direct bearing which the scientific observation or experiment has on the bedside teaching is most judiciously and carefully pointed out, and the results of recent investigations are used to make clear the fundamental changes which take place in disease.

The first part of the book is devoted to general considerations and methods of diagnosis, in which among others there are excellent chapters on the blood-pressure, the arterial and venous pulse and the electrocardiogram. In the second part "Diseased Conditions Due to Diffuse Pathological Processes" are discussed. In this section there are several chapters on cardiac overstrain, broken compensation and general symptoms of cardiac disease, excellent chapters on the general principles of treatment, the effect of drugs, gymnastics and hydrotherapy in cardiac diseases, and sections on the affections of the myocardium and the broad subject of arteriosclerosis with its results.

In the third part, the diseases of the various heart valves are treated separately, and chapters are devoted to heart block and Adams Stokes syndrome, pericarditis, wounds of the heart and aneurysm. Finally, the book closes with chapters on "Functional Diseases Without Anatomical Lesions." Each chapter is introduced with a thorough discussion of the pathological physiology of the subject. As is inevitable in a book that deals with a subject to which knowledge is still being added, one finds statements which by this time would undoubtedly be modified by the author. The paragraphs on perpetual irregularity of the heart were evidently written before the recent work had shown conclusively that this condition was due in most cases to fibrillation and not paralysis of the auricles. So, too, in the section on arteriosclerosis, the author's views as to the etiology and classification of the diseases of the blood vessels are in places not as definite as one might wish, especially as regards the syphilitic type of mesarteritis. One very excellent feature is the great number of illustrations and diagrams which help immensely to present complicated problems in an objective manner. Most of these, too, are original and afford a great relief from the hackneyed cuts so common in most text books. A selected bibliography is appended to each chapter. The monograph can be highly recommended to both students and practitioners, and whoever reads it will be sure to experience pleasure and gain much information.

A TREATISE ON DIAGNOSTIC METHODS OF EXAMINATION By Dr. Hermann Sahlh, Director of the Medical Clinic, University of Bern. Edited, with Additions, by Nathaniel Bowditch Potter, M.D., Assistant Professor of Clinical Medicine at Columbia University (College of Physicians and Surgeons), New York. Second Edition. Authorized Translation from the Fifth Revised and Enlarged German Edition. Cloth. Price, \$6.50 net. Pp. 1229, with 471 illustrations. Philadelphia: W. B. Saunders Company, 1911.

Perhaps there is no single book on diagnostic methods which has had as wide influence as this treatise of Professor Sahlh, and when we come to look for the reason, it is undoubtedly to be found in the fact that the treatise is not a mere description of methods of clinical examination, compiled from text-books and journal articles, but really a critical survey of the clinical procedures, almost all of which have been used and carefully tested in the clinic at Bern. It therefore represents actually the work of one man, and the stamp of his authority gives the book a value which it could attain in no other way. In many instances, moreover, the paragraphs on the use and value of certain instruments and methods of examination have appeared first in this book and, in a way, therefore, the treatise must be considered as an original communication. The fifth German edition has been very thoroughly revised and considerably enlarged. The chapter on hemodynamics has been entirely rewritten, and extensive revision has been made in practically every chapter in the book. These changes are particularly noticeable in the section on the examination of the stomach, the chapter on the blood, and the examination of the intestinal canal, but it is impossible here to mention in detail the various and numerous changes and additions. The American edition has been increased in size by over 200 pages, and yet some of the material in the last edition has been omitted or replaced by new matter.

In the chapter on physical diagnosis, the author describes at some length the value of the newer methods of percussion, such as the orthopercussion of Goldscheider, but rather advises against their use. There is no mention made of the third heart sound. Though the section on hemodynamics has been rewritten, and most of the modern methods of examination are critically surveyed, one is greatly astonished not to see a single word concerning the electrocardiograph, the instrument is not even mentioned. Several pages are devoted to sphygmobolometry. In the chapter on the examination of the stomach, there is a long description of the desmold reaction and the butyrometric method of the examination of the stomach contents is described much more fully than in the last edition.

In the chapter on the blood, very free use is made of Naegeli's *Blut-Krankheiten*, and most of his views on the origin of the blood-cells and the classification of diseases of the hematopoietic tissues are accepted. Considerable space, perhaps proportionately too much, is devoted to a discussion of the viscosity of the blood. The valuable chapter on the nervous system has been considerably altered and enlarged. Great credit is due to the translator and editor, for certain little inaccuracies and faults which were present in the first American edition have been corrected, and the present volume has been edited with much care and discretion. Comparatively few additions have been made, and these have been chosen most happily and almost all from the American literature. Chief among them are a note on Grocco's sign, a very useful paragraph on the collection of urine, Folin's method for the determination of acetone and acetoacetic acid, Schaffer's method for the determination of beta oxybutyric acid, methods for enumerating platelets and Noguchi's modification of the Wassermann reaction and the butyric acid test for globulins in the spinal fluid.

A curious reduplication, however, has occurred in one instance, for Folin and Schaffer's methods are described on page 603 and again almost in the same words on page 656. It may be said that the present edition is almost like a new book, so greatly has it been changed and added to, and it is now unquestionably one of the most valuable treatises on diagnostic methods which we possess.



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## PATHOLOGICAL ANATOMY OF EXOPHTHALMIC GOITER THE ANATOMICAL AND PHYSIOLOGICAL RELATIONS OF THE THYROID GLAND TO THE DISEASE, THE TREATMENT\*

DAVID MARINE, M.D., AND C. H. LENHART, M.D.  
CLEVELAND, OHIO

### 1 INTRODUCTION

The sixty-nine cases used as the basis of this report include all cases clinically diagnosed as exophthalmic goiter at Lakeside Hospital from Sept 7, 1907, to Sept 7, 1910 from which sufficient thyroid gland tissue was obtained for anatomical studies and for iodin determinations.

The principal data appertaining to each case have been tabulated as briefly as possible (Table 3). It will be noticed that special stress is laid on the objective phenomena obtained during the patient's stay in the hospital. This was done (1) because we have as yet no accurate standard of estimating the importance of subjective sensations in this disease, although they are doubtless of great importance in all nervous and mental diseases, and (2) because our major interest at present is concerned with the physiological relation of the thyroid gland to the symptom-complex.

### 2 PATHOLOGICAL ANATOMY

In describing the pathological anatomy of exophthalmic goiter we must be content at present with cataloging the changes in the various tissues of the body, in the order of their constancy and prominence. This amounts to describing the structural alterations of those tissues which biologically are endowed with the greatest means of physiological adaptability, and must necessarily leave uncharted much that may be of the greatest significance in tissues whose powers of objective manifestation of reaction are most limited. Thus it cannot be stated that, because the structural changes in the brain appear less marked than those of the lymphoid or thyroid tissues, therefore they are of less importance.

The morbid anatomy comprises changes in many organs. Indeed all the body tissues may be affected, as might be expected in a disease in which nutrition is so gravely impaired. It is on account of the attempts

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\*From the H. K. Cushing Laboratory of Experimental Medicine, Western Reserve University, Cleveland, O.

to raise the anatomical changes of certain tissues (formerly the nervous tissues, now the thyroid gland) to the rôles of primary factors that conflicting hypotheses and controversies have arisen

We are not justified in ascribing a greater or lesser degree of importance to the anatomical changes than the experimental data of morbid physiology and of morbid chemistry make possible, for, in this disease which is probably a general nutritional disturbance, it is by these means that the primary or causal alterations can be separated from the secondary or resulting alterations

## I THYROID GLAND<sup>1</sup>

Widely different views are held concerning the character of the thyroid changes. There are those who hold that the changes are constant and specific. Others hold that the thyroid changes are neither constant nor specific, while still others believe that these changes are relatively constant but in no sense specific. These differences of opinion have arisen largely from the fact that (1) many writers have used very small series of cases as the basis of their conclusions, and (2) that great differences exist depending on whether the districts in which the cases arise are goitrous or not. Thus, in the cases arising in non-goitrous districts a single anatomical type of goiter (the small, generally symmetrical gland of from 40 to 150 gm weight with uniform generalized fibrosis and active hyperplasia) predominates, while in cases arising in goitrous districts as in the Alpine districts of Austria, Italy, Switzerland and France or in the Great Lakes Basin of America, a great variety of changes are met with, e. g., nodular (adenomatous) goiters, large, hemorrhagic-cystic goiters with extensive degenerative changes and large, simple colloid goiters, as well as the first form mentioned.

We have discarded four cases of clinically diagnosed exophthalmic goiter in which the anatomical changes in the thyroid were varied and highly complicated, in order to simplify the detection and interpretation of any relation of the iodine content to the histological structure and of any relation both of the iodine content and histological structure to the disease as a whole

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1 Our studies have led us to the conclusion that the thyroid and parathyroid glands are independent structures both anatomically and physiologically. We have examined the parathyroids from nineteen patients with exophthalmic goiter, with findings similar to those reported by MacCallum, *Med News*, N. Y., 1903, p. 820, viz. That there is no anatomical or physiological evidence of any relation between the parathyroid and the exophthalmic goiter symptom complex. Recently Roussy and Clunet (*Compt rend Soc de biol*, 1910, lxxviii, 818) have reported examinations of the thyroid parathyroid apparatus in two congenital cretins who died at the ages of 25 and 28 years. They found that the lower parathyroids were normal in both patients while the upper pair was not detected in either. The thyroid lobes were extremely atrophic in one patient and absent in the other.

The thyroids of the sixty-nine cases used in this study (Table 3) are grouped as follows (1) Normal thyroids (i e, as regards gross appearance, histological structure and iodine content)—two cases (1a) Normal-colloids (that is, glands in which one could not decide from their gross appearance, their histological structure or their iodine content whether they had or had not at some previous time undergone slight hypertrophy)—three cases (2) Actively hyperplastic thyroids (i e, including all the degrees of active hyperplasia from the slightest departure from the normal or the colloid gland to extreme cellular proliferation, whether occurring on a colloid or a normal thyroid basis)—forty-three cases (2a) Premature atrophy supervening in active hyperplasia—four cases (included under hyperplasias) (3) Colloid goiters (pure type)—eighteen cases (4) Fetal or simple adenomata (pure type)—eight cases (three included with normal-colloids and two with colloids) Thus, five of the nine<sup>2</sup> great divisions of the thyroid changes are represented These five anatomical groups embrace all the known variations in the functional activity of the gland with which structural changes have been associated We have grouped these changes in the following scheme in order to bring out their sequential relations and to render the following descriptions more easily understood

- 1 Normal thyroids
- 2 Hyperplasias
  - I Primary, i e developing on a normal gland basis
    - A Developmental stage
    - B Involuntary stage
    - C Atrophic stage
  - II Secondary, i e developing on a colloid gland basis
    - A Developmental stage
    - B Involutional stage
    - C Atrophic stage
- 3 Colloid glands
- 4 Adenomata
  - I Simple
  - II Fetal
- 5 Old complicated goiters

#### 1 NORMAL GLANDS AND NORMAL COLLOID GLANDS (SEE FIG 1)

The clinical diagnosis in the two cases with normal thyroids (using the most rigid standards) and the three cases with normal-colloid thyroids (ordinarily called normal) may be questioned, since goiter (anatomical standard) was absent in all five and exophthalmos in three Such cases are not unique, however MacCallum<sup>3</sup> records such an instance

<sup>2</sup> Marine and Lenhart Pathological Anatomy of the Thyroid Gland, THE ARCHIVES INT MED, 1911, vii, 506

<sup>3</sup> MacCallum The Pathology of Exophthalmic Goiter, Jour Am Med Assn, 1907, xiv, 1158

Halsted<sup>4</sup> and others have remarked on the occurrence of the syndrome in individuals with normal glands. Such cases are ordinarily classed clinically as incomplete (*forme fruste*) exophthalmic goiter. They are more common than the literature indicates. Two possible explanations may be offered for such cases: either (1) thyroid hyperplasia was prevented by the presence of a high iodine content (a well-established fact for animals) or (2) the cases were not true exophthalmic goiter but some closely allied nervous symptom-complex, as neurasthenia or psychasthenia. Full descriptions of the anatomically normal gland have already appeared<sup>5</sup> and need not be repeated here.

## 2 ACTIVE HYPERPLASIAS (SEE FIG 2)

In forty-three cases some degree of active thyroid hyperplasia was present. The degree of hyperplasia varied from the slightest departure from normal (hypertrophy) to the marked proliferations (hyperplasia). For reasons that have been discussed in previous papers, it is necessary to divide the hyperplasias into two groups, depending on whether they develop on the basis of normal (primary) or of colloid (secondary) glands. Clinically, this division of the cases into "primary" and "secondary" exophthalmic goiter has long been used. In presenting the anatomical characteristics of thyroid hyperplasia as they are observed in exophthalmic goiter one must bear in mind that the simplest conception includes parts of three different anatomical processes and of the three corresponding functional stages, viz. (1) the developing or compensatory or hyperactive stage, (2) the involutionary or recovery or colloidal stage, and (3) the thyroid exhaustion or premature atrophy or myxedematous stage. All these stages overlap, both as to their anatomical and their physiological characteristics, so that in a given gland one may have any degree of one or more of the above named processes represented. It is preferable, therefore, to describe these stages separately although *in vivo* such a separation does not frequently exist.

### I PRIMARY HYPERPLASIA

In a majority of the cases of exophthalmic goiter occurring in non-goitrous regions and to a much less extent in those occurring in goitrous districts, the hyperplasia develops from a normal gland base. We have grouped seventeen glands in this class. It might be designated as the classical type and, since the studies based on the surgical collections have so emphasized this change to the exclusion of others, a widely held opinion has been created that the thyroid changes in exophthalmic goiter are specific.

<sup>4</sup> Halsted. Bull. Johns Hopkins Hosp., 1903, xvi, 288.

<sup>5</sup> Marine and Lenhart. Relation of Iodine to the Structure of Human Thyroids, THE ARCHIVES INT. MED., 1909 iv, 440, 1911, vii 506.



### *A The Developmental Stage*

Tracing the development of hypertrophy and hyperplasia from the normal gland, the first change noticed is the increased blood-supply. The capsular vessels, both veins and arteries, are dilated and hypertrophied. The capillaries surrounding the follicles are dilated. The gland becomes larger, softer, and takes on a brighter red color. Microscopically, there is a lessening of the stainable colloid. At first it merely stains less intensely, later vacuolization and finally a disappearance of the true colloid occurs, its place being taken by a granular albuminous debris in which may be seen leukocytes and shed epithelial cells. As the colloid disappears, the epithelial cells change from the normal cuboidal to high cuboidal, to columnar, and finally to high columnar, while preserving their uniformity and regularity. With the disappearance of the colloid and the growth in size and number of the epithelial cells, the color of the gland changes from the normal amber-red to reddish translucency, to gray-red, and finally to the soft fleshy, gray-red and opaque color of the marked hyperplasia. As true hyperplasia of the epithelial cells takes place, the existing follicles enlarge and new ones are formed, probably by budding. Infoldings and plications begin to appear and may progress so as to almost fill the space originally occupied by the colloid. This infolding of the lining epithelium is largely dependent on the capsular and stroma tension. The gland capsule and stroma hypertrophy parallel with the epithelial proliferation. In the early stages of hyperplasia, this connective tissue-hyperplasia is relatively slight, while in the later stages the interlobular bands are relatively prominent and give to the gland a mildly hobnailed appearance. Complications, as hemorrhage, cyst formation, calcification, etc., are exceedingly rare. The entire gland shares these changes. The gland is symmetrically enlarged and preserves the outlines of its original or normal state. The enlargement is, of course, variable with the degree of active hyperplasia but rarely exceeds 200 gm and, as we shall point out later, becomes smaller as fibrosis and atrophy supervene. The foci or nests of lymphoid tissue which develop in the gland stroma will be discussed under "Lymphoid Tissue."

### *B Involutionary, Recovery or Colloidal Stage*

The thyroid undergoes exceedingly rapid histological changes, both within the limits of health and of disease. These changes are for the most part of two types. (1) the developing hyperplasia, just described, and (2) its involution to the colloid state. These two processes of increased and decreased thyroid activity may alternate even from week to week, depending on different nutritional states of the body. They occur in all true goiters, in all animals, but are most pronounced in man on account of the more changeable conditions of nutrition and environment. In

exophthalmic goiter, owing to its spontaneous exacerbations and remissions, or to the treatment instituted, a progressive active hyperplasia of the thyroid is rarely allowed to continue its course undisturbed for a long time. Under such conditions the active hyperplasia ceases and may remain stationary, or it may partially involute to the colloid state, then undergo hyperplasia again, or the involution may be complete, in which case the gland returns to the pure colloid or resting stage. This in turn may be temporary or permanent, depending on the increased or decreased needs of the organism for thyroid activity. This involution, or return to the colloid state, occurs in all spontaneously recovering exophthalmic goiters (and in all other goiters as well) and invariably occurs following the administration of iodine-containing substances. It becomes obvious, therefore, that any given gland at the time of removal may be undergoing either progressive (actively hyperplastic) or regressive (involutionary) changes.

One must reckon with all degrees of this regressive or involutionary change from the marked hyperplasia back to the pure colloid gland, just as one has to reckon with all degrees of the progressive (actively hyperplastic) change from the normal or colloid gland up to marked hyperplasias. The anatomical changes are, therefore, just the reverse of those described under "developing hyperplasia" and are briefly as follows. The gland as a whole becomes firmer to the touch. The color changes from gray-red and opaque of the marked hyperplasias to gray-red and translucent, to reddish translucency and finally to the translucent amber-red color of the pure colloid gland. The blood-supply diminishes. This is associated with a lessening of the caliber of both the arteries and veins, due to a thickening of the vessel-walls similar to that observed in the involuting thymus or uterus. The follicles gradually become visible to the naked eye. They appear as enlarged, rounded cavities containing colloid—the latter at first but palely staining and granular, gradually becomes more uniform, more dense, stains more intensely and finally comes to resemble in all respects normal colloid. As the colloid accumulates the high columnar epithelium with its infoldings slowly returns to columnar, to cuboidal and finally to flat cuboidal, if the involution is complete, while the infoldings take on more of the appearance of small tufts of stroma jutting into the follicular lumen and covered with the prevailing type of follicular epithelium. Even the stroma becomes less prominent either by compression or absorption, and in the pure colloid state may show hyaline transformation. As a rule, this series of changes produces some lessening of the size of the gland as a whole. This, however, is a manifestation of minor importance.

These regressive changes may be prolonged for months or years or they may occur in a few weeks, depending on the degree of active hyperplasia existing at the time the involutionary process was instituted and

on the agents or factors underlying and producing the involution. All these changes may occur without altering the symptom-complex in any way. As a rule, however, there is some slight amelioration of the symptoms.

The question naturally arises how to distinguish and classify, anatomically, these regressive changes since, if they are the reverse of the progressive changes, corresponding degrees of either must have many anatomical features in common. They have. One may not be able to distinguish them. The iodine content is a material help, since it is usually lower in the developing hyperplasia and higher in the involutionary stage. Then a carefully taken clinical history may be of value. The greatest difficulty comes in separating these regressive changes from progressive changes occurring on a colloid base. Again the iodine content and a carefully taken history are the best aids. As regards classification, we have used the prefix 'colloid' in conjunction with the degree of hyperplasia as, e. g., "colloid-moderate hyperplasia," since the process of involution necessarily implies the colloid phase.

### *C The Exhaustion or Premature Atrophy or Myxedematous Stage*

The thyroid cells in active hyperplasia are hyperactive. If this hyperactivity is allowed to continue without periods of physiological cell-rest, the cells sooner or later die of exhaustion. While this mode of termination of an active hyperplasia may occur in any clinical form of goiter in any animal, in the adult human subject it is most commonly seen in the end stage of exophthalmic goiter (myxedema) and in children in the developing cretin. Clinically, the gradual replacement of the symptoms of exophthalmic goiter by those of myxedema has long been known, but its constant association with definite anatomical changes has not been specifically emphasized beyond the well-known clinical fact that in the late stages of exophthalmic goiter, the gland often becomes smaller and firmer. Anatomically the evidence of cell exhaustion and cell death in exophthalmic goiter is detectable before there is any clinical suspicion of a diminution of the functional activity of the gland. MacCallum<sup>3</sup> has clearly described these very early histological changes but did not point out their possible significance.

Just as one has to reckon with all degrees of 'developing hyperplasia' from the normal gland up to the markedly hyperplastic stage, and with all degrees of the "involutionary or recovery stage" from the markedly hyperplastic gland back to the colloid gland, so in premature atrophy one has to reckon with all degrees of the process from the slightest atypical cell-growth in the markedly hyperplastic gland back to the small, scar-like thyroid in which are scattered islands of compressed epithelial cells.

Tracing the process from its first manifestations in a marked active hyperplasia, the gland becomes smaller and firmer to the touch. It

remains extremely vascular. The capsule is thickened. The stroma, both inter- and intra-lobular, becomes denser and compresses the follicles. Colloid is absent. On section the gland has a dry, granular, gray-red-opaque appearance. Microscopically, the epithelial cells are at first of a uniform high columnar type with here and there an atypical cell mass. As the atrophy progresses more and more, the epithelial cells become irregular in size and shape and staining reactions. The epithelium loses its uniform arrangement in the follicles and piling up, desquamation and disintegration are seen in the same follicle along with mitotic figures. The nuclei are enlarged, often hyperchromatic, and quite variable in size, shape, and staining intensity. As the atrophic process continues, the follicles are further reduced by the cells' death and advancing sclerosis until they may appear as compressed nests of cells with or without the bare outlines of follicles. We have four mild examples of such glands in our exophthalmic goiter series in which, clinically, the severe and classical symptoms masked the definite though slight manifestations of myxedema. We have also had a specimen of this type of thyroid change referred to us with the histological diagnosis of probable cancer.

Such anatomical evidence of the inability of the cells to further grow and divide normally has long been looked on as a cell-exhaustion, the result of overwork and malnutrition, and since R. Heitwig and his pupils have produced and studied similar changes in the protozoan cell, it becomes probable that this is the true explanation.

In cretin pups we have observed thyroid changes similar to those just described and have been able to cause these atypical cells to return to the cuboidal or resting form with the accumulation of colloid in the follicles by the administration of small doses of iodine, and later, by partial removal of the gland, to produce a uniform and regular compensatory epithelial hyperplasia.

The process, therefore, whether occurring in exophthalmic goiter or in cretinism, is a premature cell death in spite of attempts to regenerate and is never observed in the early or vigorous stages of cell growth. It is of interest to note in this connection that Warthin<sup>6</sup> has described the same process of premature atrophy and fibrosis of lymph-glands in the lymphoid hyperplasia of status lymphaticus.

## II SECONDARY HYPERPLASIA

Clinically, the cases with secondary active hyperplasia are often spoken of as secondary exophthalmic goiter, while anatomically the term means only active hyperplasia developing from a colloid gland. These cases are much more common in goiter districts. In our series we have thus designated twenty-six cases. The number is probably not absolutely

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6 Warthin Arch. Pediat., 1909, xvi, 597

accurate since, as pointed out above, it most likely includes cases in which the primary or preceding hyperplasia had not returned to pure colloid goiter. The distinction, however, between primary and secondary hyperplasia is important, first, because it recognizes the fundamental conception of colloid goiter as the cured stage of an active hyperplasia and not as a degeneration, and secondly, because it offers a logical and simple explanation for many structural changes which have, in the past served as a basis for theoretical discussion.

### 1 *Developing Secondary Active Hyperplasias*

Active hyperplasias developing from colloid glands do not differ from those developing from normal glands and all gradations from the colloid gland up to the marked hyperplasia occur. Their interpretation offers

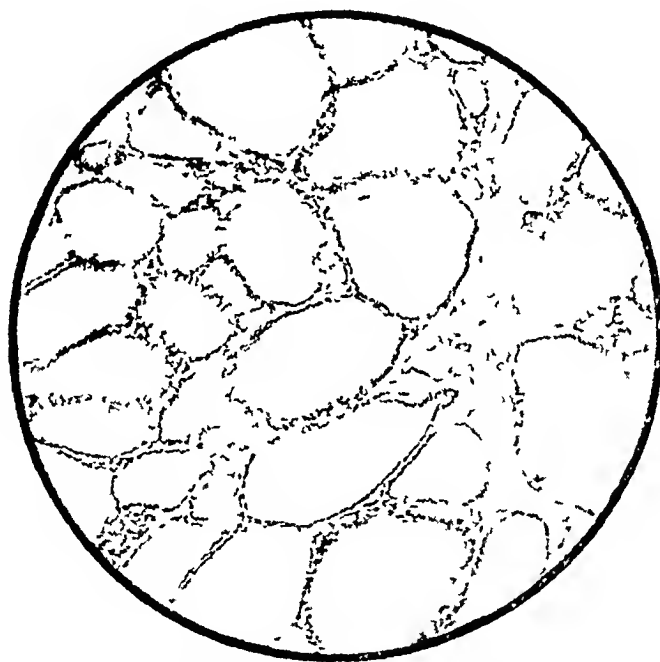


Fig. 1—Normal thyroid (Case II—450, see Table 3). Note the rounded and moderately uniform size of the follicles, the homogeneous and uniform colloid, the cuboidal epithelium and the normal stroma.

more difficulties on account of the frequency of other morphological changes. Thus it is rare to see secondary hyperplasias in man free from other structural changes as hemorrhage, cyst formation, degeneration or tumors. Then, in addition, the presence of any or all of these conditions may modify or impair the reaction of the adjacent thyroid tissue, and one not uncommonly sees in these glands large central areas or it may be but a few enlarged follicles which fail to undergo active hyperplasia, while the peripheral zone shows the usual picture of increased blood-supply, decrease in colloid and columnar epithelium with infoldings and plications.

The essential anatomical changes are the same as those detailed for the primary hyperplasia and need not be repeated since all glands with extensive complicating changes were excluded

### *B Involutionary or Recovery or Colloid Stage*

The growth of a secondary active hyperplasia may be arrested at any stage of its development and partially or completely return to colloid goiter again. The anatomical changes in this process are the reverse of those seen in the developing stage and identical with those detailed under "The involution of primary active hyperplasias." It may be pointed out here that this cycle of changes, characterized by developing hyperplasia followed by its involution, is common to all goiters and in all animals



Fig. 2—Active thyroid hyperplasia of marked degree (Case H—427 as type, see Table 3). Note the irregular sized and distorted follicles with infoldings and plications of the lining epithelium, the regular and uniform, high columnar epithelium, the absence of true colloid and the generalized increase of stroma.

studied, and one may see the cycle repeating itself in the gland again and again as is illustrated in the thyroid changes with multiple pregnancies in man, or as can be produced experimentally in dogs by alternately giving and withholding iodine in conjunction with partial removal of the gland.

### *C Exhaustion or Premature Atrophy or Myxedematous Stage*

If the secondary hyperplasia is permitted to continue without periods of physiological rest, a series of changes may occur similar to those already described as occurring in the "Exhaustion stage of primary active hyperplasia." It is not so frequent, however, as in the primary group for

the reason that the individual has as a rule much more thyroid tissue with which to compensate. Nevertheless, it may occur. In our series of glands we did not recognize such an instance.

### 3 COLLOID GOITERS (SEE FIG 3)

There are eighteen in our series. Colloid goiter is the nearest normal state anatomically (and physiologically as well), to which actively hyperplastic thyroids may return. This involution, whether it occurs spontaneously or is induced by the action of iodine, is histologically the same. The general characteristics of pure colloid goiter are (1) decreased blood-supply as compared with that which is present in the active hyperplasia, (2) an accumulation of normal colloid in the enlarged follicles, (3) a return of the follicular epithelium to the normal cuboidal form. The

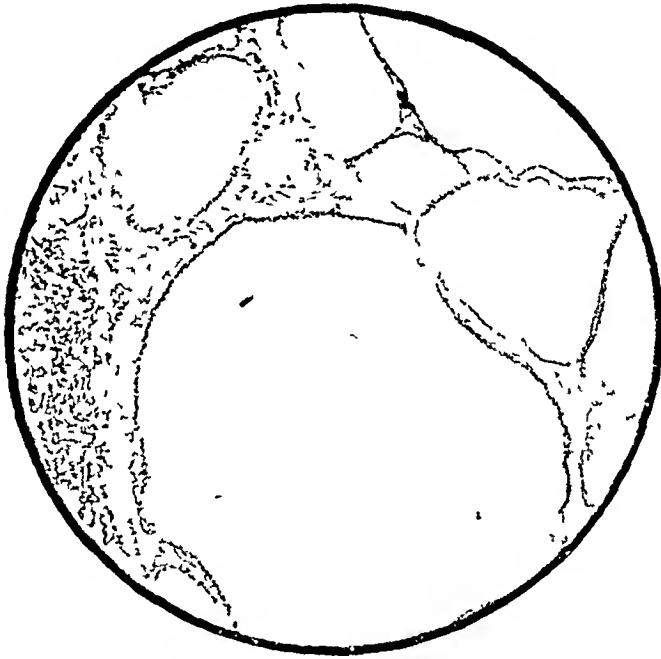


Fig. 3—Colloid goiter (Case II—236, see Table 3). Note the great variation in the size of the follicles, their slightly irregular outlines, the normal cuboidal epithelium and the uniform, normally staining colloid. Note also the focus of lymphoid tissue in the stroma and its relation to the thyroid follicles.

histological details of these changes and of the process as a whole have already been published.<sup>7</sup>

In certain of the cases with colloid goiter no past history of iodine medication was obtained, in others such a history was definite, and in still others we have personally followed its administration and the resulting thyroid changes, so that we can positively state that iodine induces the same kind of changes in the active hyperplasia of exophthalmic goiter as in any other functional hyperplasia in any of the animals studied.

<sup>7</sup> Marine and Lenhart. Bull. Johns Hopkins Hosp. 1909, 11, 131. THE ARCHIVES INT. MED., 1911, 11, 506.

This biological reaction with iodin eliminates the formerly widely held opinion among pathological anatomists that the thyroid changes in exophthalmic goiter are specific and explains such cases as that reported by Shepherd and Duval<sup>8</sup> in which at the first operation the gland was in the state of active hyperplasia and at a later operation the gland was in the colloid state, or of such cases as that reported by MacCallum,<sup>3</sup> when at a first operation there was a mild degree of active hyperplasia and at a second operation there was a more marked hyperplasia. The size of colloid goiters is usually smaller than, but depends largely on, the preceding active hyperplasia and is therefore variable.

#### 4. ADENOMATA (SEE FIG 4)

Adenomata were present in eight cases, of which six were of the fetal adenoma types. In five, the entire lobe including the tumor was removed.

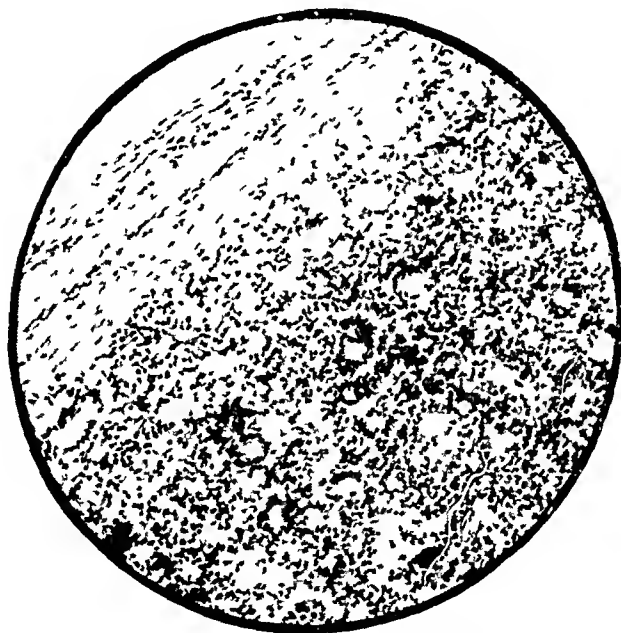


Fig. 4—Fetal adenoma (Case H—220 v, see Table 3) Showing relation of capsule to parenchyma

These glands have been grouped according to the anatomical structure of the non-tumor thyroid tissue which in three cases was that of normal colloid glands and in two cases, colloid glands. In the remaining three cases the tumors were enucleated. As pointed out in a previous paper adenomata do not occur in otherwise normal glands and the presence of colloid glands in the five instances of our series merely means that the preceding hyperplasia of the non-tumor thyroid tissue had returned to the colloid state either spontaneously or through the action of iodine, without notably affecting the tumors. The histological characteristics of both

<sup>8</sup> Shepherd and Duval. *Ann. Surg.*, 1909, 1, 84



the fetal and simple adenomata have been described elsewhere<sup>9</sup> and need not be repeated. Any direct relation of these tumors to the symptom-complex of exophthalmic goiter is doubtful since we have found several (seven in 216 autopsies) of these tumors at autopsy when no suspicion of thyroid disease existed and have also seen several specimens accidentally removed along with goiters from cases with no manifestations of exophthalmic goiter. Many authors have observed these tumors, in connection with exophthalmic goiter and Bloodgood<sup>10</sup> in this country has reported such cases, but came to the same general conclusion to which we have been led, viz, that the association is accidental and in no sense causal.

### 5 HIGHLY COMPLICATED GOITER

We will merely mention the four cases diagnosed as exophthalmic goiter, in which highly complicated old colloid goiters were removed. The structures were so disturbed by hemorrhage, cyst-formation, calcification, circumscribed tumor nodules, etc, that it was impossible to gain any conception of the relative importance of the several structural alterations.

## II THYMUS, SPLEEN AND LYMPH-GLANDS

The changes in these organs are as striking and as constant as those of the thyroid. In the past, little importance has been attached to these tissues in describing the pathological anatomy of exophthalmic goiter, although the occurrence of changes has long been noted. During recent years the lymphoid hyperplasia has attracted much attention and to-day we are forced to give to these organs a place of equal importance in the pathological anatomy of exophthalmic goiter, to that held by the thyroid. There are observers who look on lymphoid hyperplasia as a complicating factor in exophthalmic goiter—preferring to speak of exophthalmic goiter *and* lymphatism—rather than as an integral part of the same process. The constancy with which lymphoid hyperplasia occurs in exophthalmic goiter and the definite parallelism between the degree of lymphoid hyperplasia and the thyroid hyperplasia in their progressive stages, cannot now be passed as accidental. Just as the thyroid hyperplasia is not specific for exophthalmic goiter, so also the lymphoid hyperplasia is not specific. Identical changes in the thymus, spleen and lymph-glands constantly occur in status lymphaticus and frequently in cretinism, myxedema, acromegaly, myasthenia gravis, epilepsy, achondroplasia, rickets and the so-called simple goiter.

### I THE THYMUS

While Maikham first noted enlargement of the thymus in exophthalmic goiter, it was not until Marie in 1888 suggested that there might

<sup>9</sup> Marine and Lenhart. *THE ARCHIVES INT MED*, 1911, vii, 506

<sup>10</sup> Bloodgood. *Surg Gynec and Obst*, 1906, ii, 121

be a "revivescence" of the involuted thymus in exophthalmic goiter that more general interest was aroused. The more recent studies of Hait, Gierke, Thornebecke, Hektoen, Capelle, Warthin, Kocher and others have demonstrated the constancy of the thymic hyperplasia in exophthalmic goiter. The degree of hyperplasia present varies with the age of the patient, the duration and severity of the disease and most certainly with other still unknown factors. Thus, in young individuals the gland throughout is composed of elastic, grayish-pink and opaque tissue, while in older subjects there are usually accumulations of fat in the lobules, giving them a yellowish translucent appearance with patchy grayish areas of thymic tissue. Histologically, there are no distinctive features from the hyperplasia of status lymphaticus or myxedema or even the normal thymus.<sup>11</sup>

Whether regeneration of the involuted thymus occurs is difficult of actual demonstration. In support of Marie's view may be mentioned the fact (1) that the thymus in a markedly involuted state persists throughout life and (2) that the thymus hyperplasia seen in cases of exophthalmic goiter developing after 40 years of age usually has markedly reduced numbers of Hassall's corpuscles. This disproportion is probably due to the fact that Hassall's corpuscles, being only the atrophic vestiges of the thymic ducts, are incapable of regeneration.

## II SPLEEN

Splenic enlargement is the rule. This enlargement is in part due to the hyperplasia of the Malpighian corpuscles and the generalized sclerosis. The organ is firm to the touch. On section the Malpighian corpuscles are distinct and enlarged. The capsule and trabeculae are thickened. Histologically there are no distinctive features by which the splenic enlargement in goiter may be separated from those seen in the *status lymphaticus* group.

## III LYMPH-GLANDS

The lymphoid tissue increase is general. It involves both the formed lymph-nodes and the small scattered nests of lymphocytes in the framework of several viscera, as the thyroid, liver and kidney. In all the cases of exophthalmic goiter with well-marked active thyroid hyperplasia, we have observed lymph foci in the thyroid stroma. These areas vary from small collections of lymphocytes to larger areas with well-formed germinal centers. They also vary with the degree of general lymphoid hyperplasia. The Peyer's patches and solitary follicles of the small intestine and colon respectively are enlarged. The tonsils are also frequently enlarged and adenoid growths in the nasopharynx are commonly seen. Histologically, the individual lymph-follicles appear normal. In older or

11 Warthin. In Osler and McCrae's *Modern Medicine*, Phila., 1908, iv, 789.

long-standing cases there is usually a general increase in the stroma which as Warthin<sup>12</sup> has pointed out may go on to connective tissue overgrowth with atrophy and disappearance of the parenchyma cells. It will be recalled that the thyroid may undergo a similar sclerosis and atrophy of the parenchyma cells in the late stages of compensatory hyperplasia. The lymphoid elements of the bone-marrow may be increased just as occasionally occurs in lymphatism.

### III THE NERVOUS SYSTEM

The lesions thus far reported are neither constant nor suggestive of any specific gross abnormality. In the brain small hemorrhages and areas of softening are occasionally noticed. In the medulla, areas of softening and punctate hemorrhages have also been found, but with no constancy of occurrence or location. Atrophy and sclerosis of one or both testiform bodies and of the solitary tract are likewise only occasionally present. In the cervical sympathetic trunks atrophy of the ganglion cells in one or in all the cervical ganglia accompanied by fibrosis, pigmentation and small round cell-infiltration have been reported, but in a majority of the specimens examined, whether at autopsy or at operation, no lesions could be made out. The lesions of the peripheral nervous system and the spinal cord can be ascribed to the general state of nutrition and the accidental association with other diseases. The absence, however, of any constant gross lesion does not preclude the probability that the central nervous system is profoundly affected, but suggests, as Gowers<sup>13</sup> states, "that the morbid state of the nervous system is one of that finer cell-nutrition that still baffles our means of investigation."

### IV HEART

The heart hypertrophies with the development of active thyroid hyperplasia (goiter) in all animals thus far studied, including the fish, dog, sheep, ox and man. The cardiac hypertrophy in general varies with the size of the hyperplastic thyroid. The most marked and perhaps simplest type of heart hypertrophy is seen in cretins (lambs, pups and children). Taking the goitrous cretin pup as the most familiar example, it is found that the whole musculature of the heart is hypertrophied. The ventricles appear relatively more enlarged than the auricles. Both ventricles are also dilated. Histologically, the muscle is of normal appearance. The heart valves are normal. The inferior vena cava is not enlarged, while the superior cava and all its communications leading from the thyroid are dilated and their walls hypertrophied. Clinically, venous pulsation is nearly constantly present in these pups and may usually be

12 Warthin. In Osler and McCune's *Modern Medicine*, 1908, iv, 778

13 Gowers. *Diseases of the Nervous System*, Phila., 1888, p. 1211

recognized at some distance from the animal, thus showing the extent of the insufficiency of the annular orifice of the superior cava. The pulmonary artery is also enlarged. The pulmonary veins are not particularly enlarged. The aorta is enlarged as far as the left carotid branch, and it is not unusual to see the left carotid artery as large as the aorta beyond this branch. Both carotid trunks appear to terminate in the superior thyroid arteries and the internal carotids and the remaining branches of the external carotids appear as relatively small branches of these main trunks. In dogs with large goiters the much enlarged arteries are therefore mainly the thyroid arteries. We have also been able to follow the regressive changes in these arteries as the hyperplasia involutes to its colloid or quiescent state and to note the gradual lessening of the size of these arteries and the development of endo-arterial thickening with calcification (in man and sheep particularly) in the late stages. We have also observed under such conditions that the heart becomes smaller. This is the simplest manifestation of the so-called "goiter heart." It resembles in all respects the hypertrophies resulting from work, and there appears to be no reason for regarding it as different.

In human goiter the early anatomical changes as above described for dogs occur, but in the long-standing cases in adults, and particularly in exophthalmic goiter, secondary changes affecting the valves, the arteries, the myocardium and the conductivity of impulses often develop. As there are many views concerning the significance of these late changes, it would take us too far afield to consider them here.

Concluding, then, we would again emphasize that the cretinoid states in the very young animals offer the simplest and best material for the study of the uncomplicated "goiter heart," and that such studies indicate that the condition is primarily a work-hypertrophy. The secondary and subsequent changes are more intricate and perhaps dependent on a failing nutrition.

## V SKELETAL MUSCLES

Askanazy<sup>14</sup> has called attention to the general disturbance in the nutrition of the skeletal muscles. In his four cases he found, in association with the atrophy of the fibers and the loss of normal striation, fat deposits in and around the fibers which he has likened to the fatty metamorphosis seen in progressive muscular dystrophy. The occurrence of fatty changes in the eye-muscles was known to von Recklinghausen and Buschan. Profound muscular weakness is often present in this disease without corresponding reduction in the muscle bulk, and it is possible that the fatty metamorphosis is in some way related to this phenomenon.

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14 Askanazy. *Deutsch Arch f klin Med*, 1896, *lx*, 118.

## VI BONE

The development of osteomalacia during the course of exophthalmic goiter has been observed by von Recklinghausen, Haemig, Revilliod, von Jaksch and H Ratky, Hoennicke and others. The association of thyroid hyperplasia with endemic osteomalacia is well known, and it is doubtful whether the osteomalacia developing in exophthalmic goiter is of any greater or different significance than the osteomalacia with goiter in general. Both the goiter and the bone changes are probably secondary to some more general disturbance. The more prominent bone changes are decalcification, increased vascularity of the periosteum and widening of the Haversian capillaries.

## VII LIVER

In a significant number of the long-standing cases coming to autopsy, cirrhosis of the liver has been observed. In the gross such livers are reduced in volume, sometimes smooth, sometimes slightly granular and again distinctly hobnailed. The extent of the connective tissue increase varies from a slight thickening of the portal spaces to well-marked fibrous bands. The liver-cells usually exhibit some degree of fatty metamorphosis.<sup>15</sup>

## VIII BLOOD

The occurrence of high grades of chlorotic anemia is probably less common now than formerly. Bigelow<sup>16</sup> mentions its frequent association with the patients he saw in Boston and adds that in London in 1857 nothing was more common than "Pale, anemic, weak girls with goiter and staring eyes." Chvostek<sup>17</sup> has also remarked on the association. To-day, while slight degrees of the chlorotic type of anemia<sup>18</sup> are often present and while true chlorosis is usually associated with thyroid hyperplasia and often with mild manifestations of the exophthalmic goiter symptom-complex (Vnichow and Stengel), there does not appear to be any special relation between the exophthalmic goiter syndrome and the changes in the red blood-tissue. There are distinct and relatively constant, but in no sense specific, alterations in the ratios of the white blood-cells. The total number of white blood-cells is but slightly altered. As Sawyer, Kochei, Buehler, Kappis, Van Lier, Carpi and others have shown, the change is a decrease in the number of the polymorphonuclear

15 There have been six post mortem examinations of fatal cases at Lakeside Hospital (Autopsy Nos 474, 777, 966, 1131, 1171, 1211). There were four males aged 65, 55, 44 and 20 years, and two females aged 56 and 31 years. In five of the cases there was well-marked thickening of Glisson's capsule throughout the liver and in four a diagnosis of atrophic cirrhosis was made.

16 Bigelow Boston Med and Surg Jour, 1859 60, 1, 37

17 Chvostek Wien klin Wchnschr, 1893, vi, 487

18 Roth Deutsch med Wchnschr, 1910, 11, 258

leukocytes and an increase in the lymphocytes and mononuclear leukocytes Van Lier<sup>19</sup> finds in forty-five cases of true exophthalmic goiter that averages of from 8 to 10 per cent of all white blood-cells are mononuclear leukocytes and that averages of from 35 to 45 per cent of all white blood-cells are lymphocytes. Extremes of 16 per cent of mononuclears and 57 per cent of lymphocytes have been reported. We have found that there is a close parallelism between the percentage of mononuclear cells in the circulating blood and the extent of the active lymphoid and thyroid hyperplasia. The blood examination is, therefore, the most accurate clinical means of judging the extent of active lymphoid hyperplasia and, while in no sense specific for exophthalmic goiter, is a fair index of the severity of the disease.

### 3 RELATION OF IODIN CONTENT TO GLAND STRUCTURE

The published observations concerning thyroid iodin in its relation to exophthalmic goiter have shown no uniformity. The causes of these widely different results are the same as those which caused the widely

TABLE 1—IODIN CONTENTS, NORMAL SERIES

Anatomical Groups	No of Cases	Iodin per gm of Dried Thyroid in mg		
		Extremes	Mean	Average
Normals and Normal Colloids	5	4.00 0.96	1.54	1.92
Normal early glandular hyperplasia	1			0.77
Normal-moderate marked glandular hyperplasia	5	0.81 0.31	0.38	0.51
Normal-marked glandular hyperplasia	11	0.58 0.00	0.12	0.22

TABLE 2—IODIN CONTENTS, COLLOID SERIES

Anatomical Groups	No of Cases	Iodin per gm of Dried Thyroid in mg		
		Extremes	Mean	Average
Pure Colloids	18	4.61 1.00	2.24	2.24
Colloid-early glandular hyperplasia	6	0.84 0.61	0.71	0.72
Colloid early moderate glandular hyperplasia	3	0.92 0.31	0.77	0.67
Colloid-moderate glandular hyperplasia	3	0.82 0.37	0.55	0.58
Colloid-moderate marked glandular hyperplasia	3	0.82 0.32	0.34	0.49

different conclusions concerning the anatomical changes. Iodin variations are more quickly and more easily produced than structural variations. Both iodine content and gland structure are subject to rapid natural changes in all animals, and when in addition to these natural changes one has to consider the artificial variations from one cause and

19 Van Lier. Beitr. z. klin. Chir., 1910, LV, 201.

another to which human thyroids as a group, and exophthalmic goiter thyroids in particular, are subject, it becomes evident that no fundamental or general conclusions can be drawn until one has collected a large series of iodine determinations, and at the same time has a general knowledge of the natural and experimentally induced variations in man and the lower animals. Then, by excluding all glands whose structural changes are so manifold as to be reducible to some single type, it is possible to draw conclusions concerning the relation of iodine to structure

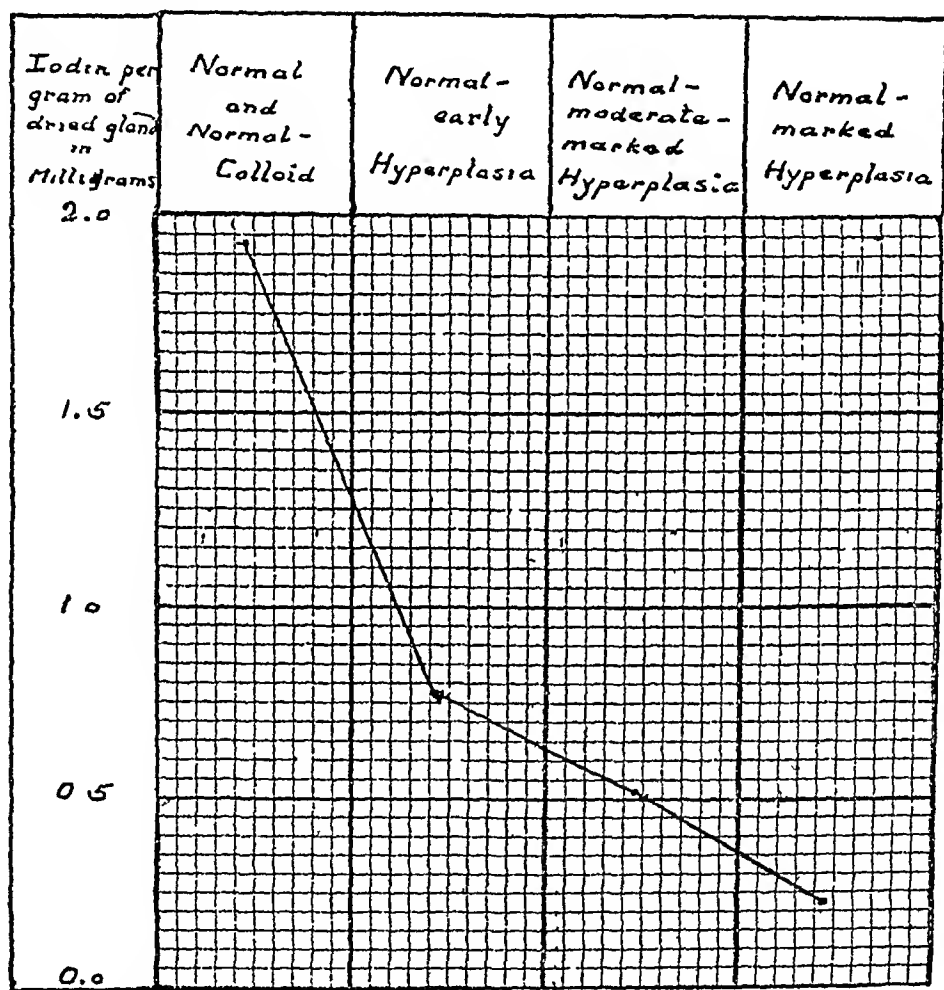


Fig 5 —Normal series, average iodine contents

In our series there were sixty-nine glands in which such comparisons were justifiable. Eleven of these glands have been excluded from the accompanying tables (Tables 1 and 2) for the reason that iodine had been given so recently (two to three weeks) that at the time of removal they were still actively hyperplastic. In three, adenomata only were removed.

An examination of these tables shows that the normal or normal-colloid and the pure colloid glands have the highest percentage iodine contents, and that the marked hyperplasias have the lowest iodine contents. In the accompanying curves (Figs 5 and 6), made from the average

percentage iodine contents, this relation is more graphically shown. Here one notes the great drop in the percentage iodine content from the normal or colloid gland which occurs before noticeable histological changes take place. This great drop is similar to that constantly found in the dog, sheep, pig, ox and human thyroid series previously reported,<sup>20</sup> and we ascribe the same significance to it as was then given for thyroids in general, viz., "that the percentage of iodine which normal or colloid

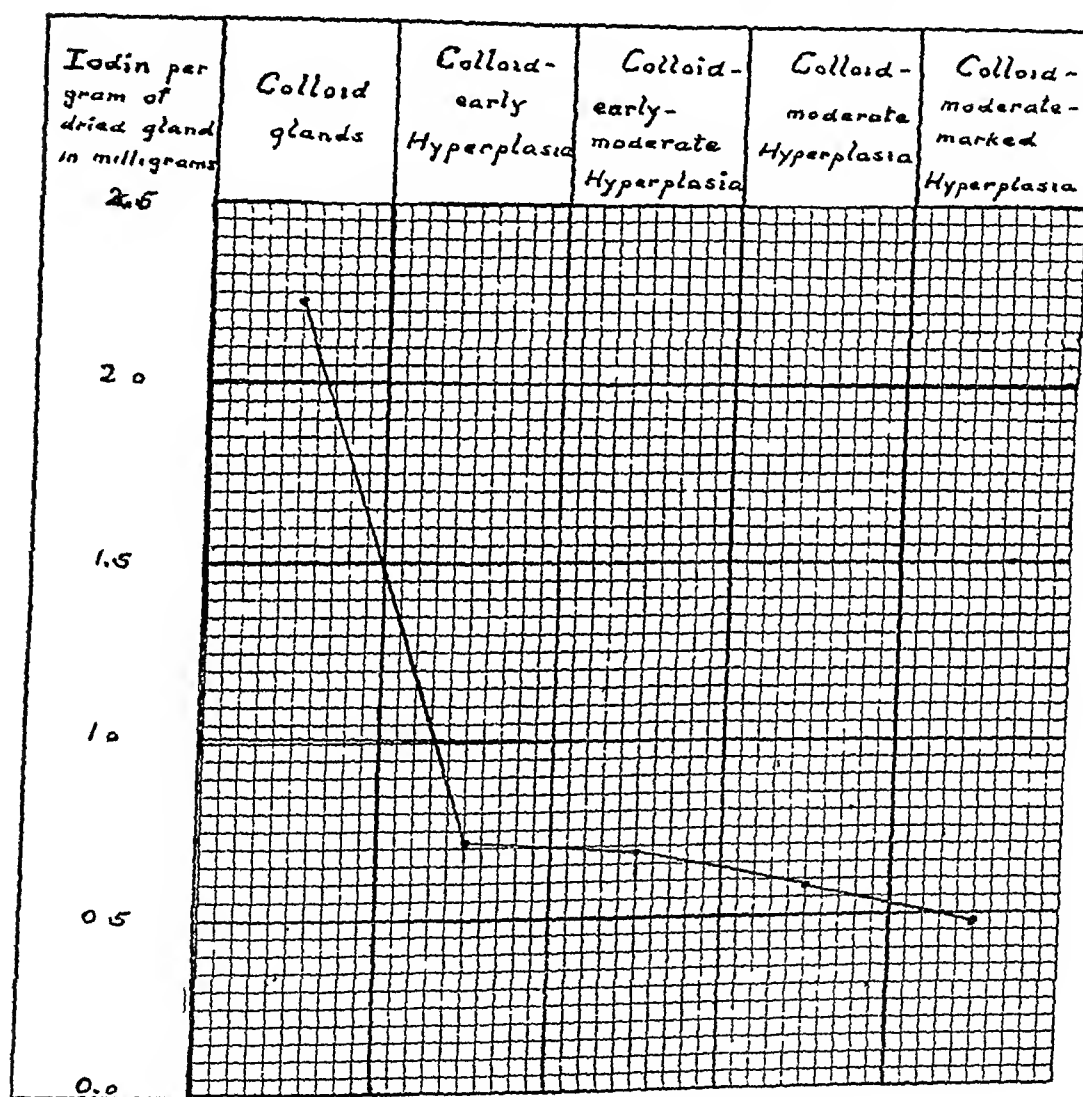


Fig 6—Colloid series, average iodine contents

thyroids may contain is variable, but the percentage necessary to maintain normal or colloid gland structure is quite constant." Passing to the several degrees of active hyperplasia, it is seen that, just as in all the lower animals and in the non-exophthalmic human series, there is a more gradual but progressive lessening of the percentage iodine content, which



reaches its lowest amount in the marked hyperplasias both of the normal and colloid series

The eight cases of exophthalmic goiter with adenomata were grouped as follows: six with the fetal adenomata and two with the simple adenomata. The iodine contents of the six fetal adenomata were 0.0, 0.0, 0.01, 0.08, 0.08, and 0.14 mg per gram of dried tumor. The two simple adenomata contained 0.25 and 0.38 mg iodine per gram of dried substance. In three of these cases the tumor alone was removed and in five a portion of the non-tumor thyroid tissue in addition was removed. A comparison of the percentage iodine contents of the tumors with those of the surrounding original thyroid tissue in each corresponding case (Table 3), shows that no relation exists between them, even in those cases (two) known to have received iodine medication. The surrounding thyroid tissue in all five cases was very high in iodine, while the tumors were very low in iodine. Thus, while the original thyroid tissue is capable of taking up iodine rapidly, the tumor tissue has no such capacity, and we have taken advantage of this fact as an aid in separating tumors from physiological hyperplasias, both clinically and anatomically.<sup>21</sup>

Summing up the relation of iodine to thyroid structure in exophthalmic goiter, it is seen that the same relations exist as were found true for other animals' thyroids and for the non-exophthalmic human thyroids as well, viz., that the percentage iodine content varies inversely with the degree of active epithelial hyperplasia. Hence, the changes in the iodine content, just as the morphological changes in exophthalmic goiter are only those common to all developing goiters in all the animals examined.

It becomes increasingly difficult to draw accurate conclusions concerning the relation of iodine to thyroid structure as one passes from the lower animals to man and from human thyroids in general to exophthalmic goiter, for the reason (1) that human goiters rarely continue their course for long undisturbed, and (2) that the thyroid is easily and quickly modified both as to structure and iodine content in a variety of ways which reach their numerical acme and complexity in exophthalmic goiter. Some of the major factors known to affect both the structure and the iodine content are rest, diet, drugs, intercurrent infection, locality, age and the duration of the disease.

Experimental observations on the effect of the administration of iodine in exophthalmic goiter are necessarily disconnected. There were eleven cases (one colloid-moderate-marked hyperplasia, seven colloid-moderate hyperplasias and three colloid-early hyperplasias) in which the patients were treated with iodine from one to three weeks prior to operation. In all of the cases, the iodine contents of the thyroids were markedly raised, and in none had complete involution to the colloid state occurred. There

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21 Marine and Lenhart. *THE ARCHIVES INT. MED.*, 1911, vii, 506

TABLE 3—CLINICAL OBSERVATIONS

Series Number, History Number, Sex, Age	Major Complaint Date of Admission	Goiter Duration, Consistency, Symmetry, General Nutrition	Myxedema Manifestations	Prominent Nervous Features	Exophthalmus	Days in Hospital Before Operation	Pulse Before Operation			
							Admission	High	Low	Average
H-427 1956 P W S Male 33	Goiter, tachycardia Jan 5, 1910	Six months, soft, symmetrical, pulsation, well nourished	No mention of	Muscular weakness, sweating, insomnia, tremor	+	6	130	130	80	95
H-382 1441 P W S Male 16	Goiter, dyspnea, tachycardia May 25, 1909	Eight yrs iodine, disappeared, reappeared 18 mos, soft symmetrical well nourished	Loss of hair	Muscular weakness, sweating, irritability, tremor	+	7	145	150	100	120
H-137 5152 P W S Male 42	Dyspnea, nervousness March 29, 1910	Five months, very small, symmetrical, firm, thrill, fair nutrition	Loss of body and scalp hair	Muscular weakness, diarrhea, tremor, restlessness	+	2	90	115	90	105
H-232 3575 P W S Male 43	Nervousness, weakness March 27, 1908	Fifteen months, very small, symmetrical, firm, thrill, emaciated	No mention of	Muscular weakness, tremor, sweating	+	4	85	120	68	87
H-141 4920 P W S Female 32	Goiter, weakness Dec 26, 1909	Eight months soft, symmetrical, small, well nourished	Marked general loss of hair	Skin flushes, sweats, muscular weakness, tremor	0	5	160	160	90	115
H-364 4116 P W S Female 31	Weakness tremor, palpitation Jan 4, 1909	17 years, cured by iodine, reappeared 5 yrs ago, operated, relapsed 3 years ago, lobe small, firm emaciated	General loss of hair, general brownish pigmentation	Mental depression, muscular weakness, tremor, diarrhea	+	2	110	120	100	110
H-251 P W S Male 24	Goiter, sweating May 19, 1908	Six years, small soft, symmetrical well nourished	No mention of	Muscular weakness, tremor, sweats, diarrhea	+	4	110	115	85	100
H-267 P W S Male 20	Palpitation July 19, 1908	Seven months soft, small, thrill, symmetrical poor nutrition	Loss of body hair	Extreme muscular weakness, diarrhea, tremor, melancholia	+	20	125	140	80	120
H-401 4626 P W S Female 33	Goiter, extreme nervousness July 26, 1909	Six months, soft, symmetrical lost 55 pounds in six months	Loss of hair	Constant vomiting, sweats, diarrhea, muscular weakness	+	77	140	160	95	140
H-214 3495 P W S Female 37	Nervousness, palpitation Feb 17, 1908	Two years, soft, symmetrical, moderate enlargement, well nourished	Skin dry, patchy pigmentation, loss of hair general	Melancholia, extreme weakness	+	5	130	140	120	125
H-222 3543 P W S Female 54	Goiter, weakness March 16, 1908	Three weeks, small, soft, symmetrical	No mention of	Melancholia, 8 months extreme muscular weakness, tremor	0	5	140	130	80	110
3369 P W S Female 23	Shortness of breath, palpitation Oct 17, 1907	Six months soft, medium sized, symmetrical, well nourished	No mention of	Skin flushes, irritability, diarrhea, weakness	+	34	120	170	70	120
H-443 5322 P W S Female 56	Goiter nervousness May 22 1910	For many years symmetrical, firm, poorly nourished	No mention of	Weakness, tremor, palpitation	+	6	120	120	90	100
H-388 4467½ P W S Female 27	Goiter nervousness June 6, 1909	*	*	*	+	13	*	*	*	*

\* Record lost

# IN CASES OF EXOPHTHALMIC GOITER

Pulse After Operation 1 High 2 Low 3 Average				Temperature Before Operation	Temp. After Oper'n 1, high, 2, low, 3, av				Anatomical Diagnosis	Iodin per Gram of Dried Gland in Milli- grams	Outcome (immedi- ate)	Remarks Portion of Gland Removed
First Day	Second Day	Third Day	Average at Discharge	Time in Hos- pital After Operation	Admission 1 High 2 Low 3 Average	First Day	Second Day	Third Day	Aver- Normal on Day Given			
135	130	115			99							
130	110	105	95	24 days	99	104 5	104 6	103 5				
132	120	110			98	101	102 5	102	9th	Trace (not measur- able)	Improved	Hemi- thyroid- ectomy
					98 7	103	103 5	103				
150	180	185			99 3							
130	140	145	95	19 days	99 7	102	104	106				
140	160	160			97 8	101	103 6	103 6	8th	Trace (not measur- able)	Improved	Double partial lobectomy
					99	101 5	103 7	104 5				
120	115	105			99 5							
105	95	95	95	11 days	99 5	101	100 5	100		0 08	Improved	Hemi- thyroid- ectomy
110	105	100			98	100	100	99 5	6th			
					98 7	100 5	100 3	99 8				
162	140	102			98 5							
110	90	70	85	8 days	98	102	102	101 5		0 12	Improved	Partial double lobectomy
130	105	85			98	98	98	99	6th			
					98 2	100	100	100				
145	150	130			98							
120	140	110	105	15 days	95	102	101 5	100 5		0 13	Improved	Hemi- thyroid- ectomy
130	145	120			98	100	100 5	99 5	12th			
					98 6	101 5	101	100				
150	180				99							
130	170			2 days	99	100	102 5			0 13	Died	Ligation of artery, small bit of lobe removed
135	178				98 2	98	99					
					99	99 5	101					
160	120	125			99 2							
105	100	90	70	15 days	99 2	102 4	102	102		0 28	Improved	Hemi- thyroid- ectomy
120	110	115			98	100 7	101	100 5	9th			
					98 1	101	101 5	101				
195	200	150	160		99 2							
160	150	90	75	4 days	102	104	103	106	108 5	0 21	Died	Hemi- thyroid- ectomy, autopsy
170	180	135	105		98	101	99	99 5	103			
					99	103	102	104	108			
					101 5					0 31	Died	Hemi- thyroid ectomy
					101 5							
					98							
					98 6							
180	200				98							
160	165			2 days	98	103	107			0 54	Died	Hemi- thyroid ectomy
170	180				97	100	104					
					97 5	102						
160					100							
132				1 day	100	99				0 58	Died	Partial double lobectomy
150					98							
					99							
					99 4							
				3 hrs	100	105				0 31	Died	Hemi- thyroid- ectomy
220					97	107 5						
					98 4							
130	112	103			98 5							
110	100	96	105	16 days	100 5	101	101	99 8		0 38	Improved	Hemi- thyroid- ectomy
120	110	100			98	100	99 5	99	9th			
					98 5	100 5	100	99 2				
				*								
				12 days						0 38	Improved	Hemi- thyroid- ectomy

\* Record lost

TABLE 3 (Continued) —CLINICAL OBSERVATIONS

Series Number, History Number, Sex, Age	Major Complaint Date of Admission	Goiter Duration, Consistency, Symmetry, General Nutrition	Myxedema Manifestations	Prominent Nervous Features	Exophthalmos	Days in Hospital Before Operation	Pulse Before Operation			
							Admission	High	Low	Average
H-433 5147 P W S Female 17	Nervousness, tachycardia March 29, 1910	Six years, soft, symmetrical, small, emaciated	General pigmentation, loss of hair	Extreme muscular weakness, sweating, tremor	+	11	130 140 100 120			
H 270 3775 P W S Male 35	Headache, vomiting July 15, 1908	Four weeks following influenza, small, symmetrical, firm, poorly nourished	No mention of	Gradual general weakness following influenza	0	6	120 125 90 105			
H-250 P W S Male 22	Loss of nervous control June 9, 1908	No thyroid enlargement, firm, well nourished	No mention of	General neurasthenia	0	4	90 95 72 90			
H-450 5369 P W S Female 20	Nervousness, tachycardia Sept 20, 1910	Palpable thyroid, firm, well nourished	No mention of	Tremor muscular weakness, sweats	+	2	104 104 80 95			
H-402 4663 P W S Male 22	Nervousness, tachycardia Sept 20, 1909	Palpable thyroid, firm, well nourished	Loss of hair	Nervousness, diarrhea	0	5	90 90 70 80			
H 434 5200 P W S Female 45	Nervousness, tachycardia April 7, 1910	Slight enlargement of right lobe two years, firm, well nourished	No mention of	Menopause, weakness, tremor	+	2	84 84 67 72			
H 239 Female 45	Nervousness, weakness April 21 1908	Two years, small mass on right side, firm, well nourished	No mention of	Muscular weakness, sleeplessness, nervousness	0	2	100 112 90 100			
H 348 4098 P W S Female 27	Dysmenorrhea, weakness Dec 5, 1908	Palpable thyroid, firm, well nourished	No mention of	Irritable neurasthenia	0	2	128 128 80 85			
H 429 4973 P W S Male 16	Dyspnea Jan 26, 1910	Nine months, symmetrical, firm, well nourished	Loss of hair	3 months noticed tremor, sweating, weakness	0	2	95 95 67 70			
H 371 4220 P W S Female 40	Goiter, dyspnea Feb 26, 1909	Twenty six years, symmetrical, firm, well nourished	No mention of	Dizziness gradual weakness for last six years	0	1	100 100 85 92			
H 372 4300 P W S Female 57	Tumor of neck March 5, 1909	Seven years mainly on right side, firm, well nourished	No mention of	Tremor irritability	0	1	90 107 90 100			
H 212 3487 P W S Female 29	Goiter Feb 4, 1908	Ten years, firm, symmetrical, well nourished	No mention of	Weakness, sweating, hysteria	0	2	80 100 70 90			

## IN CASES OF EXOPHTHALMIC GOITER

Pulse After Operation 1 High 2 Low 3 Average					Temperature Before Operation	Temp After Oper'n 1, high, 2, low, 3, av				Diagnosis Anatomical	Iodin per Gram of Dried Gland in Milli grams	Outcome (immedi- ate)	Remarks Portion of Gland Removed
First Day	Second Day	Third Day	Average at Discharge	Time in Hos- pital After Operation	Admission 1 High 2 Low 3 Average	First Day	Second Day	Third Day	Ave Normal on Day Given				
180				9 hrs	101 101 98 98.8	101				Moderate- marked glandular hyperplasia	0.69	Died	Hemi- thyroid- ectomy, weight, 35 gm
180 120 150	190 120 160	140 110 125	80	10 days	98 99 98 98.2	100.5 99 100.2	100 99 99.2	100 98 99	4th	Moderate- marked glandular hyperplasia	0.81	Improved	Hemi- thyroid- ectomy
130 110 120	137 110 120	135 120 130	95	11 days	98 99 97 98	102 100.5 101	102 101 101.5	99.5 98 99	5th	Normal early glandular hyperplasia	0.77	Improved	Partial double hemi- thyroid ectomy, wt of tissue removed, 13 gm
132 100 110	120 105 112	110 85 95	80	14 days	100.4 100.4 97.5 98.6	101.6 98.3 99.5	100 99 99.5	99 98 98.6	4th	Normal thyroid	1.54	Improved	Hemi- thyroid- ectomy, wt of portion removed, 12 gm
130 110 120	120 105 110	130 100 115	90	13 days	99 99 97.5 98	102.5 100 101	101 100 101	101 100 100.5	6th	Normal thyroid	4.00	Improved	Hemi- thyroid- ectomy, wt of gland, 16.5 gm
100 90 98	105 90 100	85 78 80	82	21 days	99.5 99.5 98 98.2	99.5 99 99.3	99.6 99 99.5	99 98 98.8	4th	1 Normal colloid (senile type) 2 Fetal aden- oma	0.96 0.01	Improved	Hemi- thyroid- ectomy, wt of tissue removed, 10 gm
150 120 125	125 112 120	120 110 115	80	14 days	98.6 99 98.6 98.6	100.2 99.1 100	101.2 99.6 100.5	101.2 100 100.5	8th	1 Normal colloid 2 Fetal aden- oma	1.19 0.14	Improved	Partial hemi- thyroid- ectomy
115 95 112	120 115 117	120 100 110	80	22 days	99.5 99.5 97.5 98.6	100.5 99 100	101 100 100.5	101 100 100.5	7th	1 Normal colloid 2 Fetal aden- oma	1.92 0.00	Improved	Hemi- thyroid- ectomy
125 100 110	130 100 115	110 95 100	90	12 days	100 100 97 98.7	103 101 102	104 102 103	103 101 102	7th	Pure colloid	1.00	Improved	Hemi- thyroid- ectomy
130 110 125	120 97 110	115 95 105	100	12 days	98.2 98.4 98 98.2	102 100 101	100.5 100 100.3	100 98 99	4th	Pure colloid	1.08	Improved	Hemi- thyroid- ectomy
135 120 125	133 120 125	125 120 123	90	35 days	98.2 98.2 97.5 98	103 99 101	103.4 102 103	104 102 103.5	11th	1 Pure colloid 2 Simple aden- oma	1.15 0.25	Improved	Hemi- thyroid- ectomy
110 90 100	155 90 120	140 120 130	85	12 days	98 99 97 98.2	103 99 101	102.5 101 101.5	101.5 100 100.5	6th	Pure colloid	1.28	Improved	Hemi- thyroid- ectomy

TABLE 3 (Continued) —CLINICAL OBSERVATIONS

Series Number, History Number, Sex Age	Major Complaint Date of Admission	Goiter Duration, Consistency, Symmetry, General Nutrition	Myxedema Manifestations	Prominent Nervous Features	Exophthalmus	Days in Hospital Before Operation	Pulse Before Operation		
							Admission	High	Low
H-447 P W S Female 17	Goiter, palpitation Sept 8, 1910	Six months, right lobe larger, firm, well nourished	No mention of	Mother dead, of exophthalmic goiter, weak, fidgetable	0	1	130	130	75
H 409 4805 P W S Female 55	Nervousness Nov 3, 1909	Ten years, small, firm, symmetrical, well nourished	Loss of hair	Neurotic for years, sweating, tremor	0	3	115	115	90
H-3255 P W S Female 31	Palpitation Sept 5, 1907	Twenty years, firm, symmetrical, well nourished	No mention of	Periods of melancholia, weakness, tremor	0	4	95	95	70
H-406 4776 P W S Female 38	Goiter, nervousness Oct 22, 1909	Sixteen years, small, firm, symmetrical, well nourished	No mention of	Tremor, excitable for eighteen months	+	11	120	130	80
3668 P W S Female 29	Rheumatism, palpitation, organic heart lesion Nov 6, 1907	Six months, hard, small, symmetrical, well nourished	No mention of	Always nervous, broken compensation of heart	+	1	70	90	70
3456 P W S Female 22	Goiter, abdominal pain Jan 7, 1908	Eight years, firm, symmetrical, well nourished	No mention of	Always nervous, "blues"	0	3	100	100	84
H-411 4725 P W S Female 20	Goiter, nervousness Oct 16, 1909	Four years firm, symmetrical, adenoids, well nourished	No mention of	Always nervous, palpitation	0	4	108	108	90
H 445 5487 P W S Male 56	Weakness, mental deterioration Sept 8, 1910	18 mos ago noticed small symmetrical enlargement, firm, emaciated	Loss of hair, general pigmentation	Profound weakness mental aberration	+	2	108	108	87
H-204 G S S Female 22	Goiter Jan 5, 1908	Eight years, firm, large, emaciated, well nourished	None	Typical example of relative cure of exophthalmic goiter	+	2	96	110	88
H-390 4596 P W S Female 18	Tumor of neck Aug 17, 1909	Three years, symmetrical, firm, well nourished	Slight loss of scalp hair	Somewhat nervous and weak	0	2	136	136	110
H 359 P W S Female 32	Goiter nervousness Jan 21, 1909	Seven months, soft, small, symmetrical, well nourished	No mention of	Paroxysmal palpitation and nervous weakness	0	5	110	120	72
H-203 3441 P W S Female 24	Hoarseness, goiter Dec 30, 1907	Ten years, symmetrical, small, firm, well nourished	No mention of	Tremor for four months	+	5	100	120	68
H-419 4823 P W S Female 37	Goiter, nervousness Nov 11, 1909	Twenty years, right side larger, firm, well nourished	No mention of	Weakness, excitability, slight tremor	0	11	160	160	95
H-236 3612 P W S Female 19	Goiter, nervousness April 6, 1908	Four years symmetrical, firm, well nourished	No mention of	Weakness, tremor, sweating, flushing	+	5	175	175	88

# IN CASES OF EXOPHTHALMIC GOITER

Pulse After Operation 1 High 2 Low 3 Average					Tempera- ture Before Operation	Temp After Oper'n 1, high, 2, low, 3, av				Anatomical Diagnosis	Iodin per Gram of Dried Gland in Milli- grams	Outcome (immedi- ate)	Remarks Portion of Gland Removed
First Day	Second Day	Third Day	Average at Discharge	Time in Hos- pital After Operation		First Day	Second Day	Third Day	Aver Normal on Day Given				
104 90 95	100 85 95	95 70 80	75	11 days	99.5 99.5 98 98.6	100.5 99.8 100	100.2 99 99.5	99.5 98.6 99	4th	Pure colloid	1.54	Improved	Hemi- thyroid- ectomy
160 130 150	165 135 150	160 140 150	100	25 days	98.6 99 98 98.2	103 101 102	103 101 102	102.5 100.5 101	7th	Pure colloid	1.85	Improved	Partial thyroid- ectomy
160 140 150				1 day	99.6 99.6 97.7 98	102.5 100 102				Pure colloid	1.88	Died	Hemi- thyroid- ectomy
160 135 150	170 140 160	165 140 150	105	13 days	98 98.6 97 98	102 99 100	101 100 100.5	101.5 101 101.5	10th	Pure colloid	2.00	Improved	Hemi- thyroid- ectomy
95 80 90	90 80 85	90 80 85	85	12 days	98.6 98.8 98.2 98.6	100 99 99.5	100 99 99.5	99.5 98 98.5	3d	Pure colloid	2.18	Improved	Hemi- thyroid- ectomy
135 110 120	135 120 125	120 105 115	100	18 days	99 99 98 98.2	102 101 101.5	102 101 101.5	102 99.5 100	10th	Pure colloid	2.31	Improved	Partial thyroid- ectomy
160 90 100	145 130 140	135 125 130	115	9 days	98 99 97.8 98.6	101 98 99	101 100 100.5	100.5 98 100	7th	Pure colloid	2.31	Improved	Hemi- thyroid- ectomy
130 85 128				1 day	98 98.6 97 97.5	102				Pure colloid	2.38	Died	Hemi- thyroid- ectomy, arterial ligation in May, '10
140 120 130	143 120 130	143 120 130	85	12 days	98 99 99.8 98.6	101.5 100 101	101.8 100.2 101	101.2 98 100	3d	Pure colloid	2.58	Improved	Hemi- thyroid- ectomy, fed iodine 7 months, chloro- form
135 130 131	160 115 135	140 130 135	105	12 days	99 99 98 98.6	100.5 99 99.5	101 98 100	101.5 98 100	9th	Pure colloid	2.74	Improved	Partial double thyroid- ectomy
112 100 108	120 93 108	120 109 112	105	11 days	98.5 99.6 97.5 98.2	100.4 99 100	100.8 100 100.4	100.2 99 100	4th	1 Pure colloid 2 Fetal aden- oma	2.77 0.08	Improved	Hemi- thyroid- ectomy, fed iodine
132 110 120	130 115 120	120 95 105	80	15 days	99 99.5 98 98.6	101 100 100.5	102 100 101	100.5 99 99.5	6th	Pure colloid	3.09	Improved	Hemi- thyroid- ectomy, fed iodine
130 120 125	145 120 130	160 145 155	120	15 days	99 99 98 98.6	101.5 99 101	102 100 101	102 100 101	5th	Pure colloid	3.69	Improved	Partial double lobectomy, typical lymphoid infil- tration
130 120 128	145 120 140	142 130 135	105	14 days	98 98 98 98	102 101 101.5	101.5 100 101	102 100 100.5	8th	Pure colloid	4.61	Improved	Hemi- thyroid- ectomy, fed iodine 5 months

TABLE 3 (Continued) —CLINICAL OBSERVATIONS

Series Number, History Number, Sex Age	Major Com plaint Date of Admis sion	Goiter Duration, Consist- ency, Symmetry, General Nutrition	Myxedema Manifestations	Prominent Nervous Features	Exophthalmus	Days in Hospital Be- fore Operation	Pulse Before Operation			
							Admission	High	Low	Average
H-431 5023 P W S Female 35	Goiter, nervousness Feb 18 1910	Fifteen years, nodular, firm, well nourished	No mention of	Slight general weakness	+	1	95	95	85	90
H-425 4943 P W S Female 24	Abdominal pain, nervousness Jan 5, 1910	Several years, symmetrical, mod firm, well nourished	No mention of	Migraine tremor	0	1	96	96	85	86
H-211 3486 P W S Female 36	Goiter Jan 28, 1908	Eighteen months, firm, small, symmetrical, well nourished	No mention of	Always had "blues," irritable, tremor	0	2	90	90	70	80
3461 P W S Female 20	Nervousness Jan 9, 1908	Three years, firm symmetrical, well nourished	Pigmentation	Tremor four years, excitable	+	7	115	115	85	95
H-262 3483 P W S Female 32	Tumor of neck Jan 30, 1908	Eleven years, firm symmetrical, well nourished	No mention of	Muscular weakness, tremor	0	2	95	98	75	85
H 418 4801 P W S Female 23	Goiter, nervousness Nov 12, 1909	Many years, firm symmetrical, well nourished	No mention of	General weakness	0	4	90	100	80	90
H 349 4107 P W S Female 40	Headache Nov 24, 1908	Nine months, symmetrical, small, soft, well nourished	Loss of hair, slight pigmentation	Weakness, headache excitability, vomiting	+	23	130	135	100	120
H-201 3426 P W S Female 25	Nervousness, palpitation Nov 11, 1908	Seven years, small, firm, symmetrical, well nourished	No mention of	Tremor for seven years sweating, excitable	+	27	100	130	90	100
H 391 4569 P W S Female 33	Tumor of neck July 30, 1909	Duration ? Firm, small, symmetrical, well nourished	No mention of	Mild general nervousness	0	4	115	115	85	95
H-397 4579 P W S Female 14	Goiter Aug 4, 1909	Eight years, soft, large, symmetrical, well nourished	No mention of	Very slight general nervousness	0	14	110	110	60	80
H-444 5490 P W S Female 36	Nervousness, palpitation, goiter Aug 22, 1910	Twenty five years, soft, symmetrical, well nourished	No mention of	Nervousness Excitable twelve years, muscular weakness	0	2	98	98	80	87
H-439 5210 P W S Female 16	Nervousness, goiter May 21 1910	Two years, soft, symmetrical well nourished	Loss of hair	Palpitation sweating, tremor	+	1	90	110	80	90
H 369 4234 P W S Male 22	Goiter Feb 8, 1909	Two years, soft, symmetrical well nourished	No mention of	None of note	0	3	88	88	72	80
H-394 4506 P W S Female 19	Headache, nervousness July 16, 1909	Duration ? Well nourished	No mention of	Three months, weakness, sweating, tremor	0	5	100	100	70	75
3381 P W S Female 54	Goiter and breast tumor Nov 1, 1907	Two years mod firm symmetrical, emaciated	No mention of	General weakness and nervousness	0	8	100	110	90	115



# IN CASES OF EXOPHTHALMIC GOITER

Pulse After Operation 1 High 2 Low 3 Average					Temperature Before Operation	Temp After Oper n 1, high, 2, low, 3, av				Anatomical Diagnosis	Iodin per Gram of Dried Gland in Milli grams	Outcome (immedi- ate)	Remarks Portion of Gland Removed
First Day	Second Day	Third Day	Average at Discharge	Time in Hos- pital After Operation	1 Admission High Low Average	First Day	Second Day	Third Day	Aver Normal on Day Given				
100 85 90	100 95 90	90 80 85	85	9 days	98 5 98 6 98 98 5	100 5 98 5 100	100 99 99 5	99 98 98 6	3d	Colloid- early glandular hyperplasia	0 62	Improved	Hemi- thyroid- ectomy
96 87 90	100 87 90	90 87 88	90	21 days	99 8 99 8 99 5 99 6	102 100 5 101	101 100 5 100 8	100 5 100 100 1	7th	Colloid- early glandular hyperplasia	0 62	Improved	Hemi- thyroid- ectomy
105 85 90	90 75 85	90 75 82	85	18 days	98 2 98 2 97 98	100 5 99 99 2	99 5 98 99	99 1 99 99	5th	Colloid- early glandular hyperplasia	0 65	Improved	Hemi- thyroid- ectomy
130 135 145	140 115 125	120 110 115	95	13 days	99 5 99 5 98 98 6	101 5 101 101 5	101 100 100 5	99 5 99 99 2	6th	Colloid- early glandular hyperplasia	0 77	Improved	Hemi- thyroid- ectomy
100 85 95	110 100 100	105 95 100	90	15 days	98 2 98 2 97 98	100 5 99 100	99 98 98 5	100 5 98 99	4th	Colloid- early glandular hyperplasia	0 83	Improved	Hemi- thyroid- ectomy
110 100 105	130 105 115	120 95 110	95	12 days	98 6 99 5 98 98 6	101 99 5 100	100 5 100 100	100 98 6 99 2	7th	Colloid- early glandular hyperplasia	0 85	Improved	Hemi- thyroid- ectomy
160 135 150	150 140 148	148 130 140	115	18 days	98 5 99 5 97 5 98 6	103 100 101 5	103 5 102 102 5	103 5 101 102	8th	Colloid- early glandular hyperplasia	1 85	Improved	Hemi- thyroid- ectomy, fed iodine 2 weeks
175 145 145	155 135 140	140 120 130	90	21 days	98 2 100 97 98	101 99 100	101 5 100 101	101 5 99 5 100	7th	Colloid- early glandular hyperplasia	4 12	Improved	Hemi- thyroid- ectomy, fed iodine 3 weeks
160 130 150	140 130 135	140 120 125	100	18 days	99 99 98 98 6	101 5 100 101	101 5 100 100 5	101 5 100 101		Colloid- early glandular hyperplasia	4 15	Improved	Hemi- thyroid- ectomy, no history of iodine R?
110 90 103	120 105 110	125 95 110	100	7 days	100 5 100 5 98 98 6	99 6 98 6 99 99 5	101 99 99 5	100 99 99 5	4th	Colloid- early moderate glandular hyperplasia	0 31	Improved	Hemi- lobectomy
120 100 115	112 100 105	105 90 100	90	19 days	98 5 99 98 98 5	101 99 100	100 99 99 5	99 5 98 99	8th	Colloid- early moderate glandular hyperplasia	0 77	Improved	One lobe and isthmus, entire portion of other lobe
125 110 115	120 100 110	100 80 95	80	13 days	99 5 99 5 98 5 99	100 99 5 100	101 98 5 99 6		2d	Colloid- early moderate glandular hyperplasia	0 92	Improved	Hemi- thyroid- ectomy
140 72 120	130 110 120	105 95 100	85	28 days	98 99 97 5 98 1	103 99 101	102 5 100 5 101	101 99 5 100	13th	Colloid- moderate glandular hyperplasia	0 37	Improved	Hemi- thyroid- ectomy
120 110 115	120 90 100	100 80 90	85	4 days	98 8 99 97 5 98 6	101 5 100 101	101 99 100	99 5 98 4 99	3d	Colloid- moderate glandular hyperplasia	0 55	Improved	Hemi- thyroid- ectomy
160 140 150	140 105 130	135 110 120	95	21 days	99 100 5 98 98 2	103 100 101 5	102 99 100	99 98 98 6	3d	Colloid- moderate glandular hyperplasia	0 82	Improved	Hemi- thyroid- ectomy

TABLE 3 (Continued) —CLINICAL OBSERVATIONS

Series Number, History Number, Sex Age	Major Complaint Date of Admission	Goiter Duration, Consistency, Symmetry, General Nutrition	Myxedema Manifestations	Prominent Nervous Features	Exophthalmus	Days in Hospital Before Operation	Pulse Before Operation			
							Admission	High	Low	Average
H-265 P W S Female 37	Goiter, tachycardia Aug 22, 1908	Many years, irregular nodules, firm, fair nutrition	No mention of	Weakness, nervousness, arrhythmia	+	8	110	125	80	115
H-386 4490 P W S Female 59	Tumor of neck June 13, 1909	35 years, up and down course, nodular, firm, well nourished	No mention of	Tremor, weakness	0	11	120	150	105	115
H-381 10246 G S S Female 42	Exophthalmic goiter May 28, 1909	Six years, soft, symmetrical, well nourished	No mention of	Extreme muscular weakness, tremor	+	4	115	115	70	90
H-292b 9493 G S S Male 44	Graves' disease Sept 7, 1908	Left lobe enlarged, soft, poor nutrition	Loss of hair, dry skin	Cardiac arrhythmia, weakness	+	1	90	115	82	90
H-416 1817 P W S Female 22	Goiter, nervousness Nov 1, 1909	Six months, small, soft, symmetrical, well nourished	Loss of hair	Nervousness, excitability, sweating	+	15	125	125	100	110
H-292a 9310 G S S Male 44	Graves' disease June 22, 1908	Seven months, small, firm, symmetrical, fair nutrition	Dry skin, loss of hair	Muscular weakness, mental depression, restlessness	+	26	100	115	70	80
H-269 3894 P W S Female 21	Palpitation July 27, 1908	16 mos just after typhoid fever soft, symmetrical, poorly nourished	Loss of hair	Muscular weakness, restlessness	+	14	130	135	80	90
H-392 4596 P W S Female 30	Goiter, vomiting Oct 9, 1909	Nine months, large, firm, symmetrical, poorly nourished	Loss of hair, dry skin	Nervousness, tremor, vomiting weakness	+	23	140	140	100	105*
H-264 3824 P W S Female 19	Weakness tachycardia July 3, 1908	One year, soft, symmetrical, well nourished	No mention of	Always nervous, weak, diarrhea	+	8	140	140	70	100
H-374 4898 P W S Female 26	Nervousness Feb 27, 1909	Six months soft, symmetrical, well nourished	No mention of	Tremor, diarrhea, excitability	+	19	140	140	90	125
H-215 3529 P W S Female 29	Palpitation, sweating Feb 18, 1908	Two years, pregnancy, firm, symmetrical, well nourished	No mention of	Muscular weakness, excitability, tremor, diarrhea	0	4	145	145	105	115
H-408 4692 P W S Female 36	Goiter, nervousness Oct 5, 1909	Sixteen years, enlarged isthmus, firm, well nourished	No mention of	Nervous for two years	0	1	85	90	70	80
H-417 4837 P W S Female 28	Goiter, nervousness Nov 19, 1909	Six years, firm, right lobe enlarged, well nourished	No mention of	General nervousness	0	2	130	130	90	110
3343 P W S Female 30	One sided goiter Oct 21, 1907	Twelve years, firm right side, well nourished	No mention of	General weakness, slight dyspnea	0	1	80	85	75	75

\* After one week

# IN CASES OF EXOPHTHALMIC GOITER

Pulse After Operation 1 High 2 Low 3 Average					Temperature Before Operation	Temp After Oper'n 1, high, 2, low, 3, av				Anatomical Diagnosis	Iodin per Gram of Dried Gland in Milli- grams	Outcome (immedi- ate)	Remarks Portion of Gland Removed					
First Day	Second Day	Third Day	Average at Discharge	Time in Hos- pital After Operation		1 Admission	2 High	3 Low	4 Average					First Day	Second Day	Third Day	Aver- Normal on Day Given	
185				1 day	98 102 98 100.5					105				Colloid- moderate glandular hyperplasia	1.15	Died	Hemi- thyroid- ectomy	
130	128	138		108	99.5 99.5 98 98.8					101	102.2	101.5	11th	Colloid- moderate glandular hyperplasia	1.31	Improved	Partial double lobectomy	
100	120	120	20 days		98 98.8					100	101	100						
125	125	125								100.5	102	101						
212				16 hrs	99 99 98 98.6					106				Colloid- moderate glandular hyperplasia	1.31	Died	Partial double lobectomy	
142	144	128		85	99 99 97.3 98.2					101.5	102.5	101.2	7th	Colloid- moderate glandular hyperplasia	1.85	Improved	One half of remain- ing lobe	
120	123	88	19 days		97.3 98.2					100	101.2	100.4						
130	150	106								101	101.8	100.8						
160	160	140		120	99 100 97 98.6					102	102	100	4th	Colloid- moderate glandular hyperplasia	2.00	Improved	Hemi- thyroid- ectomy	
100	140	120	17 days		97 98.6					98	100	99						
150	150	135								101	101	99.5						
170	150	110		95	99 99.5 98.0 98.2					101	101	99.5	4th	Colloid- moderate glandular hyperplasia	2.02	Improved	Hemi- thyroid- ectomy	
130	120	90	14 days		98.0 98.2					99	99	98.5						
135	135	100								100	100	99						
180				3 hrs	98 98.6 98 98.2					107				Colloid- moderate glandular hyperplasia	4.03	Died	Partial thyroid- ectomy Fed iodine one week	
140	145	140		85	98.6 98.6 98 98.6					101	101.5	101.5	4th	Colloid- moderate-marked glandular hyperplasia	0.32	Improved	Hemi- thyroid- ectomy	
120	125	125	19 days		98 98.6					100	100.5	100						
130	135	130								100.5	101	101						
128	128	104		80	101 101 98 99					100.5	100.2	99.5	4th	Colloid- moderate-marked glandular hyperplasia	0.34	Improved	Hemi- thyroid- ectomy	
110	110	100	18 days		98 99					100	99.5	98						
115	115	102								100.2	100	99						
172	170	168		130	99.6 99.6 97.5 98.6					101.2	102	100.5	11th	Colloid- moderate-marked glandular hyperplasia	0.82	Improved	Hemi- thyroid- ectomy, weight, 58 gm	
135	140	148	18 days		97.5 98.6					99	101	99.5						
160	160	160								101	101.5	100						
160	145	140		100	99 99.5 97.5 98.2					101	100.5	101	4th	Colloid- moderate-marked glandular hyperplasia	1.30	Improved	Hemi- thyroid- ectomy Fed iodine	
140	140	120	18 days		97.5 98.2					99	100	98						
150	142	130								100	100	100						
105	112	115		80	98 98.6 97.5 98.6					101	100.5	100	7th	Fetal adenoma (cells highly irregular —cancer?)	0.00	Improved	Adeno- mectomy	
95	95	95	12 days		97.5 98.6					99.5	99	100						
100	105	105								100	100	100						
135	155	142		95	99.5 99.5 98.4 98.6					101.5	101.5	100.5	7th	Colloid adenoma	0.38	Improved	Adeno- mectomy	
95	135	130	21 days		98.4 98.6					97.5	100.5	99.2						
120	140	138								99	101	100						
105	95	100		75	99 99 98.2 98.6					101.2	100.5	100.5	5th	Fetal adenoma	0.08	Improved	Adeno- mectomy	
90	85	70	11 days		98.2 98.6					100	99.5	99						
98	90	85								100.5	100	99.5						

were four cases which had received iodine for periods varying from two months to eighteen months, and in all complete involution to the colloid state was present at the time of the operation. We can, therefore, reasonably conclude that the active hyperplasia of exophthalmic goiter has the same characteristic of rapidly taking up iodine that characterizes all other active functional thyroid hyperplasias, and also that iodine induces a similar series of morphological changes in the exophthalmic goiter hyperplasia as in other active thyroid hyperplasias, and that these changes are histologically identical with those occurring in spontaneous involution (recovery).

#### 4 RELATION OF PULSE-RATE TO GLAND STRUCTURE

A tabulation of the pre-operative and postoperative pulse-rates of the sixty-nine patients is given in the large table (Table 3). We have recorded the length of time in the hospital before operation, the pulse on admission, the highest, the lowest and the average pulse records during this time. Postoperative, we have recorded the highest, lowest and average pulse-rates for the first three days, the average pulse-rate at discharge and the length of time in the hospital after operation. We believe these records should accompany all case reports, for it is by taking into account these features that an accurate idea of the types of cases, surgically treated at the various clinics, may be gained. Such tabulations bring out many features of interest and significance. Thus, it will be noticed that the pulse-rates on admission and the highest pulse-rates before operation are closely related, while the average pulse-rates are usually much lower. The higher pulse-rate on admission is a manifestation of the general nervous instability and of the loss of vagus control, while the much lower average pulse-rate illustrates the effect of rest and the extent of the recovery of vagus control.

There are such differences between the highest and the lowest pulse-rates even in the most severe cases that only the mean or average rate gives a fair conception of the cardiac activity. Thus, in our extreme cases the average for the series was 110 beats per minute, although there were individual high averages of 140, 125, 120, etc. In order to demonstrate whether any relation exists between thyroid structure and the pulse-rate, we have charted the average pulse-rates of the normal and colloid series both before and after operation (Figs 7 and 8).

In the normal series it is seen that there is a general relation between thyroid structure and the average pulse-rates. Thus, the average pulse-rates before operation are the lowest in those cases with normal glands (eighty-two per minute) and the highest (104 per minute) in the marked hyperplasias. The same relation tends to hold through the postoperative reaction as well. The difference between the pulse-rates of the cases with

normal thyroids and of those with markedly hyperplastic glands is of slight degree only, while the anatomical differences are extreme. Another feature of the pulse-rate curve is that the postoperative reaction usually reaches its extreme height in from twenty-four to forty-eight hours, then, in favorable cases it falls rapidly during the next three or four days and then continues at a more constant rate. In our cases the average pulse-rate at discharge corresponded closely with the average pulse-rate before operation. Thus, objectively the cardiac activity after operation and up

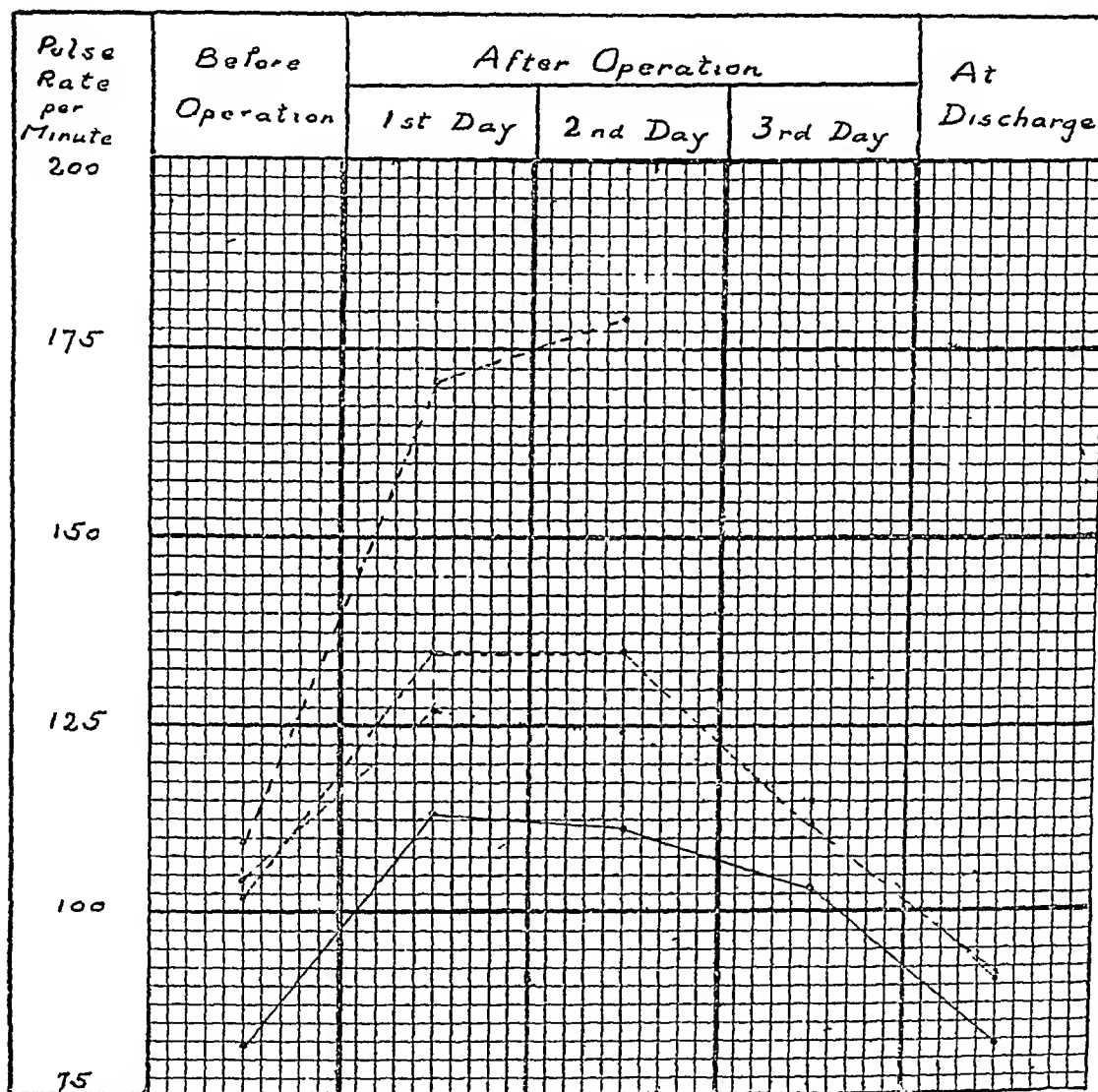


Fig 7—Normal series average pulse-rates. Plain line indicates normal thyroids. Line of dashes indicates moderate marked glandular hyperplasia. Finely dotted line indicates marked glandular hyperplasia. Line of dots and dashes indicates fatal cases.

to the time of discharge shows no noteworthy decrease from the average obtaining before operation. On the other hand, many of the patients subjectively feel a sense of cardiac relief, but as Graham Lusk has well said, "subjective sensations cannot be used as scientific criteria."<sup>22</sup>

<sup>22</sup> Lusk, Graham. Science of Nutrition, Phila., 1906, p. 244.

Passing to the colloid series, the same striking features are present as have been pointed out for the normal series, viz, the pulse-rate to a very slight extent increases with the degree of active hyperplasia, the average pulse-rate before operation closely conforms with the average pulse-rate at discharge from the hospital and the postoperative rise describes the same type of curve

Summing up the relation of the pulse-rates to the degree of active thyroid hyperplasia both in the normal and colloid series, it is seen that a slight parallelism exists, but the differences between the pulse-rates of the normal or colloid glands and of the most marked active hyperplasias are so slight as to bear no suggestion of any cause or effect relation This

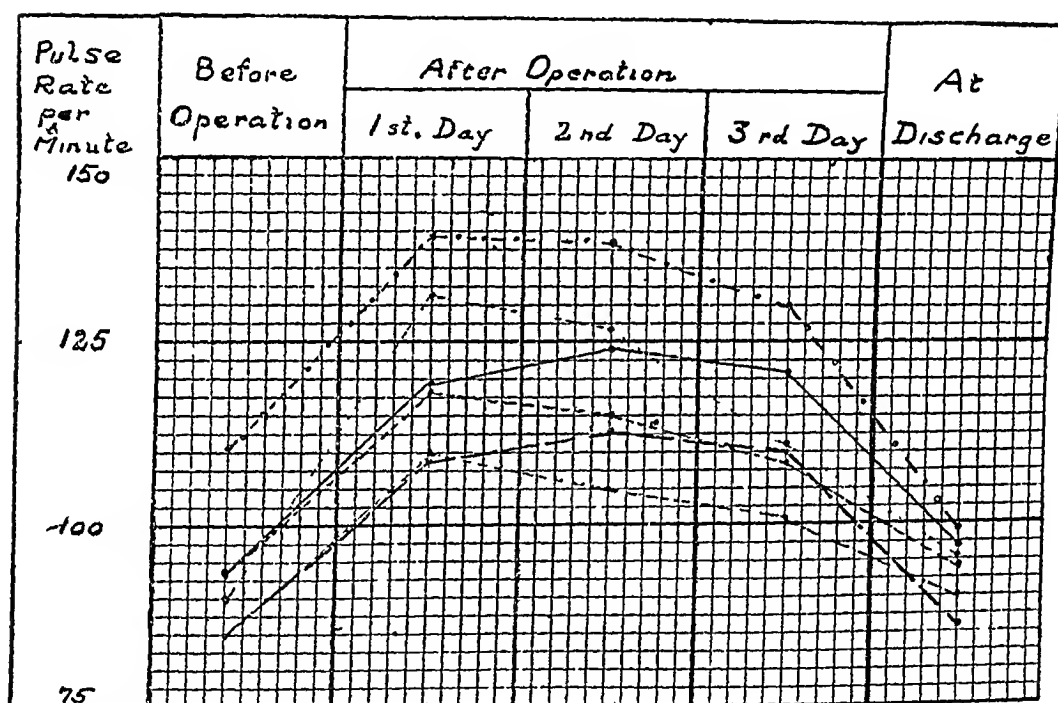


Fig 8—Colloid cases, average pulse rates Plain line indicates colloid glands Line of dashes indicates colloid early glandular hyperplasia Line of dashes and dots indicates colloid early moderate glandular hyperplasia Dotted line indicates colloid moderate glandular hyperplasia Line of dashes and circles indicates colloid moderate marked glandular hyperplasia Line of long dashes indicates adenomata

is the more striking on account of the widely held view that the thyroid secretion is a direct causal factor in the cardiac reaction If any relation exists the objective evidence would tend to indicate a hyposecretion rather than a hypersecretion, since the pulse-rate bears no relation to the amount of secreting surface and a negligible relation to the histological structure of the gland Also the histological structure and the iodine content may

be reversed in a given case, as will be mentioned later, without necessarily producing any modification of the cardiac activity, and adenomata may be associated with the same pulse reaction as ordinary hyperplasia

It does not appear from the evidence at present available that the explanation of the cardiac activity is so superficial or simple as either a thyroid-hypersecretion or hyposecretion would indicate, but that both the cardiac activity and the thyroid reaction are parallel manifestations consequent on some more general and remote disturbance

### 5 RELATION OF TEMPERATURE TO GLAND STRUCTURE

The temperature on admission, the highest, the lowest and the average temperature before operation, also the highest, lowest and average temperatures for the first three days following operation are recorded in Table 3. We have also added the total number of days of pyrexia following operation for each case

These temperatures are for the most part oral and, therefore, only of relative value. The average temperatures before operation are approximately normal in the several anatomical groups of each series. The temperatures on admission are often somewhat elevated and it frequently happens that they coincide with the highest temperatures before operation, just as was true of the pulse-rates. True fever, after rest in bed is established, is exceedingly rare in uncomplicated cases, as many observers have pointed out. The subjective sensation of fever is very common.

The postoperative rise is usually quite abrupt. It reaches its height on the second day and in favorable cases gradually falls to an average of normal in from six to eight days (average). The temperature perhaps tends to be higher in the cases with marked thyroid hyperplasia than in the cases with normal or colloid glands, just as was noted with the pulse-rates, but the differences are too slight for a suggestion of any causal relation between gland structure and temperature reaction. The slightly higher temperatures associated with the more marked hyperplasias are probably parallel phenomena and indicative of a more severe type of disease. The pulse and temperature reactions after operation constitute the so-called "manifestations of hyperthyroidism", that is, they are believed to be due to an excess of "toxic" thyroid secretion. The evidence for this hypothesis is at present inadequate. Both the temperature and pulse reactions point toward some more profound disturbance in the innervation of the nerve-centers controlling these activities than could be explained by acute variations in the amount of thyroid secretion discharged from the gland.

## 6 RELATION OF EXOPHTHALMOS TO THYROID STRUCTURE, TO MORTALITY AND TO THE DISEASE IN GENERAL

Exophthalmos was recorded as present in thirty-five and as absent in thirty-four cases. Arranging the cases according to the anatomical divisions of the thyroid, it is found that exophthalmos was present in one of eight cases with adenomata, in two of five cases with normal or normal-colloid glands, in six of eighteen cases with colloid goiters and in twenty-seven of forty-three cases with active hyperplasia. Thus, exophthalmos was neither absent from any of the anatomical divisions nor present in all the cases of any single division. The greatest number of positive cases (both absolute and percentage) occurs in the group of active hyperplasias. On further analysis it is found that the frequency of exophthalmos in this series increases as the degree of active thyroid hyperplasia increases, both in the colloid and in the normal series. Exophthalmos was present in ten and absent in two of the fatal cases.

So far as this series of cases is concerned, one may say that exophthalmos is a highly inconstant feature. A Kocher<sup>23</sup> in a series of seventy-four cases found exophthalmos in sixty-three. The personal factor, the liberality of the observer in diagnosing exophthalmic goiter and the natural facial outlines in many patients are conditions that materially modify the frequency of exophthalmos in any individual series. Only a most general relation exists between the incidence of exophthalmos and the degree of thyroid hyperplasia. Some observers have considered exophthalmos as dependent on the thyroid hyperactivity and cite the hyperthyroidization observations of Ballet and Enriquez<sup>24</sup> and of Nott-hafft,<sup>25</sup> who claim to have reproduced the symptom-complex of exophthalmic goiter in a dog and in a man, respectively, by feeding them excessive amounts of thyroid gland. While symptomatically hyperthyroidization may to some extent simulate the symptom-complex of exophthalmic goiter, it is biochemically quite different. The one might be looked on as an artificial excess of the normal secretion, while the other could not have a closer resemblance than that of a quantitative excess of an abnormal secretion.<sup>26</sup>

23 Kocher, A. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1902, *xv*, 1.

24 Ballet and Enriquez. *Semaine Méd.*, 1894, *xiv*, 66.

25 Nott-hafft. *Centralbl. f. inn. Med.*, 1898, *xix*, 353.

26 In a previous publication (Marine and Williams. *THE ARCHIVES INT. MED.*, 1908, *i*, 349) it was shown that the hyperplastic thyroid takes up iodine rapidly from inorganic and organic salts of iodine and from feeding thyroid. The general symptoms produced depend on the form and the amount of iodine given and on the anatomical state of the thyroid at the time of its administration. Overfeeding with desiccated or fresh sheep's thyroid produces the same general symptoms whether the thyroid is normal, colloid or hyperplastic, while iodine or its inorganic salts tends to produce these symptoms only in those cases



The facts that exophthalmos may be present either with the thyroid normal or with any degree of active thyroid hyperplasia, and that there may be marked thyroid hyperplasia without exophthalmos, point strongly against the view that thyroid hyperplasia is etiologically related to exophthalmos and toward the view that both phenomena are parallel, though often not synchronous, manifestations of a more fundamental and obscure nutritional disturbance

## 7 THE RELATION OF EXOPHTHALMIC GOITER TO MYXEDEMA

In our series of sixty-nine patients four (Nos 214, 222, 232, 364) had distinct anatomical changes characteristic of premature or myxedematous atrophy supervening in marked hyperplasias. In two of the patients there was well-marked general pigmentation with loss of scalp and body hair. In the other two no mention was made of these features. In the first two cases there was also dryness of the skin of the legs and arms, with sweating of the palms of the hands and soles of the feet (personal observations). Three died following operation with high temperatures and pulse-rates.

Owing to the fact that one seldom sees mention of this important and relatively frequent late manifestation in exophthalmic goiter, we would urge again the importance of very careful inquiry and examination of all cases of exophthalmic goiter coming under observation in order to detect clinically these very mild and very early manifestations of supervening myxedema, as well as careful anatomical examinations of the thyroid for the characteristic histological changes.

Old<sup>27</sup> was perhaps the first to point out that myxedema was a natural sequel rather than a complication of exophthalmic goiter. More recently C. P. Howard,<sup>28</sup> West,<sup>29</sup> Dock<sup>30</sup> and ourselves<sup>31</sup> have emphasized this view

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with very large, actively hyperplastic thyroids. These symptoms are increased appetite, loss of weight, diarrhea, becoming bloody in the late stages, weakness and sometimes coma before death. We have never observed any noteworthy increase in heart-rate or rise of body temperature or thyroid enlargement or exophthalmos in dogs, following such experiments. Cunningham (*Jour Exper Med*, 1898, *iii*, 148) in his much earlier and more extensive studies on "Experimental Thyroidism" was unable to reproduce in any of the animals used a condition resembling exophthalmic goiter by feeding thyroid gland, and at that time clearly pointed out the inadequateness of a hyperthyroidization theory in explaining the essential features of exophthalmic goiter. Recently Carlson, Rooks and McKie (*Proc Am Physiol Soc*, 1911, *xxvii*, 13) have reported their experiments with feeding thyroid to a large series of animals with the same results reported by Cunningham and ourselves.

27 *Ord Brit Med Jour*, 1885, *i*, 896

28 Howard, C. P. *Jour Am Med Assn*, 1907, *xlvi*, 1226

29 West. *St Bartholomew's Hosp Rep*, 1906, *xlii*, 9

30 Dock. In Osler's *Modern Medicine*, Phila., 1909, *vi*, 437

31 Marine and Lenhart. *Relation of Iodin to the Structure of Human Thyroids*, *THE ARCHIVES INT MED*, 1909, *iv*, 440

We have collected reports of cases by twenty-four observers and, as Hirschl<sup>32</sup> suggests, the cases may roughly be divided into two groups, (1) myxedema occurring during and (2) myxedema occurring after exophthalmic goiter. This grouping is purely clinical. The thyroid insufficiency starts when thyroid hyperplasia starts and may develop rapidly, as in cases reported by Osler,<sup>33</sup> Sollier,<sup>34</sup> Jolly<sup>35</sup> and others, in which case the severe manifestations of both symptom-complexes are nearly synchronous, or slowly, as in cases reported by Williams,<sup>36</sup> Gautier<sup>37</sup> and others, in which case the overlapping of the two syndromes is less complete.

It is of significance that myxedema never precedes but accompanies or follows exophthalmic goiter, and also, as pointed out by Gowan,<sup>38</sup> that the incidence of myxedema of adults as regards sex is the same as that of exophthalmic goiter (six to one). Clinically, it has been shown by Bence and Engel,<sup>39</sup> van Lier,<sup>40</sup> Carpi<sup>41</sup> and others that the mononuclear leukocytes and lymphocytes are increased in myxedema just as in exophthalmic goiter, and it has long been known that, anatomically, the lymphoid tissue changes are similar in both syndromes. Another observation of interest in this connection is the experience of clinicians generally that the cretin, the exophthalmic goiter or the myxedema patient has lowered resistance toward bacterial infections and Marbé<sup>42</sup> and Fassin<sup>43</sup> have demonstrated a lessening of the alexic activity of the blood-serum in both exophthalmic goiter and myxedema, and also that this lessening is the reverse of what obtains following the administration of iodine or desiccated thyroid. We have already described the anatomical features of the special form of atrophy that supervenes in the marked hyperplasia as myxedema develops and have pointed out that it may often be detected in advance of definite clinical manifestations. The iodine relations which obtain in these special atrophies of cretinism or myxedema are naturally only a continuation of the gradual lessening which characterizes the several degrees of hyperplasia.

It is generally stated that myxedema is the antithesis of exophthalmic goiter. This is based largely on the subjective and symptomatic manifestations and the fact that the manifestations of exophthalmic goiter are most pronounced during the early or developmental stage of the thyroid

32 Hirschl *Wien klin Wchnschr*, 1900, xiii, 622

33 Osler *Jour Nerv and Ment Dis*, 1899, xvi, 65

34 Sollier *Rev de Méd*, 1891, vi, 1000

35 Jolly *Jour Am Med Assn*, 1899, xxii, 814

36 Williams *Brit Med Jour*, 1893, i, 799

37 Gautier *Rev méd de la Suisse Romande*, 1898, viii, 625

38 Gowan *Lancet*, London, 1895, i, 478

39 Bence and Engel *Wien klin Wchnschr*, 1908, xxi, 905

40 Van Lier *Bertr z klin Chir*, 1910, lxx, 201

41 Carpi *Berl klin Wchnschr*, 1910, xlvii, 2059

42 Marbé *Compt rend Soc de biol*, 1909, lxxvii, 362

43 Fassin *Compt rend Soc de biol*, 1909, lxxvi, 457

hyperplasia, while manifestations of myxedema occur during the atrophic stage. The biological or objective phenomena of the physiology, the anatomy and the chemistry of the thyroid in exophthalmic goiter and myxedema, as we have shown, are closely interwoven. The fundamental conception and demonstration of myxedema or cretinism as the result of the lessening of the physiological secretion of the thyroid is the most thoroughly established fact in the pathological physiology of the thyroid. We would emphasize that the essential thyroid disturbance in myxedema is a lessening of the physiological value of the secretion and not necessarily a quantitative lessening, since a majority of all animals from fish to man have or have had enlarged thyroids both in cretinism and in myxedema. To use the words of Morel "Goiter is one stage on the road to cretinism or myxedema." Morel's dictum might, in the light of recent work, be modified to read "Active hyperplasia is the first manifestation of thyroid insufficiency," for the reason that we now know that an animal may be cured of any general disturbance of which the goiter is a manifestation and still have an enlarged thyroid (colloid goiter), in the same sense that an animal with rickets may recover, although the bone deformities persist.

Faure<sup>44</sup> has tersely put the kernel of the whole argument as follows "If myxedema is due to a deficiency, and exophthalmic goiter to an excess, of thyroid secretion, then both syndromes could scarcely coexist in the same individual." But it is now known that the two syndromes overlap to a greater or lesser extent in all of the cases of exophthalmic goiter in which the impairment of thyroid function is allowed to continue unchecked.

Horsley<sup>45</sup> has pointed out that nervousness and tremor are quite constant manifestations of the early stage of myxedema and that the reason we do not observe it more often is that the patients present themselves with the disease well advanced. He<sup>46</sup> also described a nervous, excitable stage in the thyroidectomized monkeys preceding the development of the more characteristic symptoms of cachexia strumipriva. Later McGarrison<sup>47</sup> noticed and carefully recorded a nervous stage preceding the classical manifestations of endemic cretinism in the Gilgit and Chitral Districts of India.

We believe that further study will reveal the frequent existence of nervous manifestations of the exophthalmic goiter type during the developmental stage of myxedema, just as anatomical studies have shown that

44 Faure *Presse méd*, 1899, 11, 174

45 Horsley *Brit Med Jour*, 1885, 1, 381

46 Horsley *Proc Roy Med and Chir Soc*, London, 1886, 21, 6

47 McGarrison *Proc Roy Med and Chir Soc*, London, 1908, 11, No 3, Med Sect, p 1

the thyroid tends toward and usually does undergo hyperplasia prior to the development of the myxedema complex

Loss of scalp and body hair and caries of the teeth are almost constant accompaniments of frank exophthalmic goiter. Pigmentation of the skin, either general or local, is also commonly observed. Many of our most severe cases clinically have shown no wasting of the subcutaneous tissues, while in others the wasting was extreme. We have been led to look on these manifestations as the very earliest and mildest of the series of symptoms which characterize developing myxedema.

In this connection we wish to report the major features of a typical case which we have been allowed to follow through the courtesy of Prof J. P. Sawyer and Dr. A. N. Dawson, since it embodies the most characteristic events in the course of exophthalmic goiter.

The patient, a girl aged 18, presented herself at Charity Hospital in October, 1908, with all the cardinal symptoms of exophthalmic goiter. She was admitted to the hospital and improved rapidly during the five weeks of rest and general medical treatment. She then returned to her work but relapsed during the following May and was readmitted to Charity Hospital in June, 1909. At this time the right thyroid lobe was removed. The operation was followed by the typical pulse and temperature reaction, the pulse reaching 160 and the temperature 105 degrees. Five weeks after leaving the hospital she was again admitted with typhoid fever. This disease ran an uncomplicated course but was prolonged and during the third week of convalescence it was noticed that the pulse was becoming more rapid and the remaining thyroid lobe was enlarging. She left the hospital in November, 1909, and was not seen until March, 1910, when she presented the following picture. She had gained thirty pounds. The subcutaneous tissues were everywhere thickened. The skin was dry, save for sweating of the palms of the hands and the soles of the feet. There was nearly complete loss of the body and scalp hair and the decay of the teeth had progressed rapidly. The pulse was regular and averaged 120 beats per minute. The remaining thyroid lobe had enlarged until it exceeded the size of the combined lobes before operation. Menstruation had not occurred since the typhoid fever. A diagnosis of supervening myxedema was made and as there was a great excess of very actively hyperplastic thyroid tissue present, iodine in the form of the syrup of the iodide of iron 0.3 c.c. three times daily was given. At the end of two months the remaining thyroid lobe was firm, much reduced in size and had completely involuted to the colloid or resting stage. A new growth of scalp, axillary and pubic hair developed, menstruation began again during the third month and the thickened subcutaneous tissues returned to their normal appearance. The exophthalmic goiter symptom complex, though somewhat ameliorated, is still present (Dec. 28, 1910), (pulse 110, tremor, exophthalmos and a small firm left thyroid lobe).

This case illustrates the usual way in which myxedema is associated with exophthalmic goiter. It also illustrates that it is possible to relieve the myxedema symptom-complex by the use of iodine alone, if sufficient active thyroid tissue is present and that by relieving the myxedema and by completely reversing the histological state and iodine content of the thyroid, only slight amelioration of the exophthalmic goiter symptom-complex took place.

# 8 RELATION OF POSTOPERATIVE MORTALITY TO THE ANATOMICAL CHANGES IN THE THYROID AND LYMPHOID TISSUES AND TO THE IODIN CONTENT OF THE THYROID

Complete data on which to estimate the true postoperative mortality are not available. The published statistics, of which the following are examples, Dunhill,<sup>48</sup> eighty-eight cases with 1.1 per cent mortality, the Mayos,<sup>49</sup> 405 cases with 4.7 per cent mortality, Kocher,<sup>50</sup> 494 cases with 3.4 per cent mortality, Krecke,<sup>51</sup> 108 cases with 9 per cent mortality, Hale White,<sup>52</sup> eleven cases with 36 per cent mortality, H. Mackenzie,<sup>53</sup> thirteen cases with 38 per cent mortality, and Gebele<sup>54</sup> thirty-six cases with 19 per cent mortality, show greater variations than could likely be attributed to operative skill and at the same time omit those data which are known to be most indicative of the severity of the cases, viz., the histological condition of the thyroid and lymphoid tissues. Mortality statistics based on the total number of cases clinically diagnosed as exophthalmic goiter give no accurate idea of the real mortality (1) because different observers exercise different degrees of liberality in diagnosing exophthalmic goiter, (2) because such statistics convey no idea of the stage or the severity of the disease, and (3) because the collected autopsy reports show that the mortality is greatest in those patients with marked thyroid and lymphoid hyperplasia. Unless the histological condition of the thyroid and the lymphoid tissues, together with the pulse-rate and temperature reactions both before and after operation are given, no estimate of the operative risk and the types of cases subjected to operation can be gained.

We have grouped all cases as postoperative deaths which have died within four days after operation with high temperature and pulse-rates, believing that greater error is introduced in attributing death in these cases to one or another of the many possible accompanying diseases or accidents.

Of the sixty-nine cases included in this study, twelve or 17.4 per cent died—ten females and two males (see Table 3).

The mortality arranged according to the four major anatomical groups of thyroid changes is as follows: three<sup>55</sup> cases with adenomata with no mortality, five cases with normal or normal-colloid glands with no mor-

48 Dunhill *Brit Med Jour*, 1909, 1, 1222

49 Mayo, C. H. *Surg, Gynec and Obst*, 1909, viii, 237

50 Kocher *Brit Med Jour*, 1910, ii, 931

51 Krecke *Munchen med Wchnschr*, 1909, lvi, 15

52 White, Hale *Quart Jour Med*, 1910, iv, 89

53 Mackenzie, H. *Brit Med Jour*, 1910, ii, 935

54 Gebele *Beitr z klin Chir*, 1910, lxx, 20

55 The five other cases with adenomata are included under normal colloid or colloid glands (see Table 3)

tality, eighteen cases with pure colloid goiters with two deaths, or a mortality of 11 per cent, and forty-three cases with active hyperplasia with ten deaths, or a mortality of 23 per cent. It is thus seen that the highest mortality occurs in the group of active hyperplasias and by arranging the ten fatal cases of this group according to the degree of active hyperplasia present, it is found that all were associated with advanced degrees of active hyperplasia.

The symptoms, as we are at present able to interpret them, offer inconstant and unreliable criteria of severity and risk of operation except in those cases with manifestations of supervening myxedema, which are the greatest operative risks. Three of our four patients died following operation. Thus, it may be stated at present that the thyroid and lymphoid hyperplasia offer the most constant criteria of severity and that the mortality varies with the degree of hyperplasia of these tissues.

Concerning the relation of mortality to the iodine content, there is no literature bearing directly on this feature, although it could be inferred that since the mortality is greatest in those cases with marked hyperplasia, and since iodine normally varies inversely with the degree of hyperplasia, that the mortality would be highest in those cases with low iodine content. The accompanying tabulation of nine<sup>56</sup> of the fatal cases bears out this inference (see Fig 9).

There are three general hypotheses as to the cause of the phenomena of high pulse-rates, high temperatures and death in these cases: (1) that they are the result of squeezing an excess of thyroid secretion into the organism from gland manipulation at operation, (2) that they are the result of status lymphaticus, (3) that they are the result of the general state of exhaustion and weakness of the organism.

Taking up the first hypothesis, Putnam<sup>57</sup> suggested it in order to explain the phenomena on the basis of a hyperthyroidization theory. It is still widely held by those who think both the temperature and pulse reactions are the result of a hyperthyroidization, but there is now sufficient evidence to render it untenable, first because the operative mortality is greatest in those patients with small, cirrhotic glands and low iodine content, and is least in those patients with excessive thyroid tissue and high iodine content. This is the opposite of what should obtain if the secretion caused the symptoms and iodine determined the secretion's major activity. Second, the gravest risks are those patients with symptoms of

<sup>56</sup> Three fatal cases (Cases 269, 381 and 265) have been excluded because iodine was administered for too short an interval before operation for corresponding histological changes to occur. Thus, the iodine contents were 4.02, 1.31 and 1.15 mgm per gram of dried gland, while the histological diagnosis in these cases was colloid-moderate hyperplasia, and experience has shown that such iodine contents can coexist with such degrees of active hyperplasia only in cases in which insufficient time has elapsed since the administration of iodine began.

<sup>57</sup> Putnam, *Brain*, 1894, xvii, 214.

myxedema supervening on the exophthalmic goiter syndrome Third, these phenomena of high temperature, high pulse-rate and death occur as well after arterial ligation as after lobectomy Fourth, operations elsewhere on the body or trauma or shock are, with proportionate frequency, followed by these phenomena Thus, Crile<sup>58</sup> has reported a patient dying after ether anesthesia alone and cites a patient dying from the shock

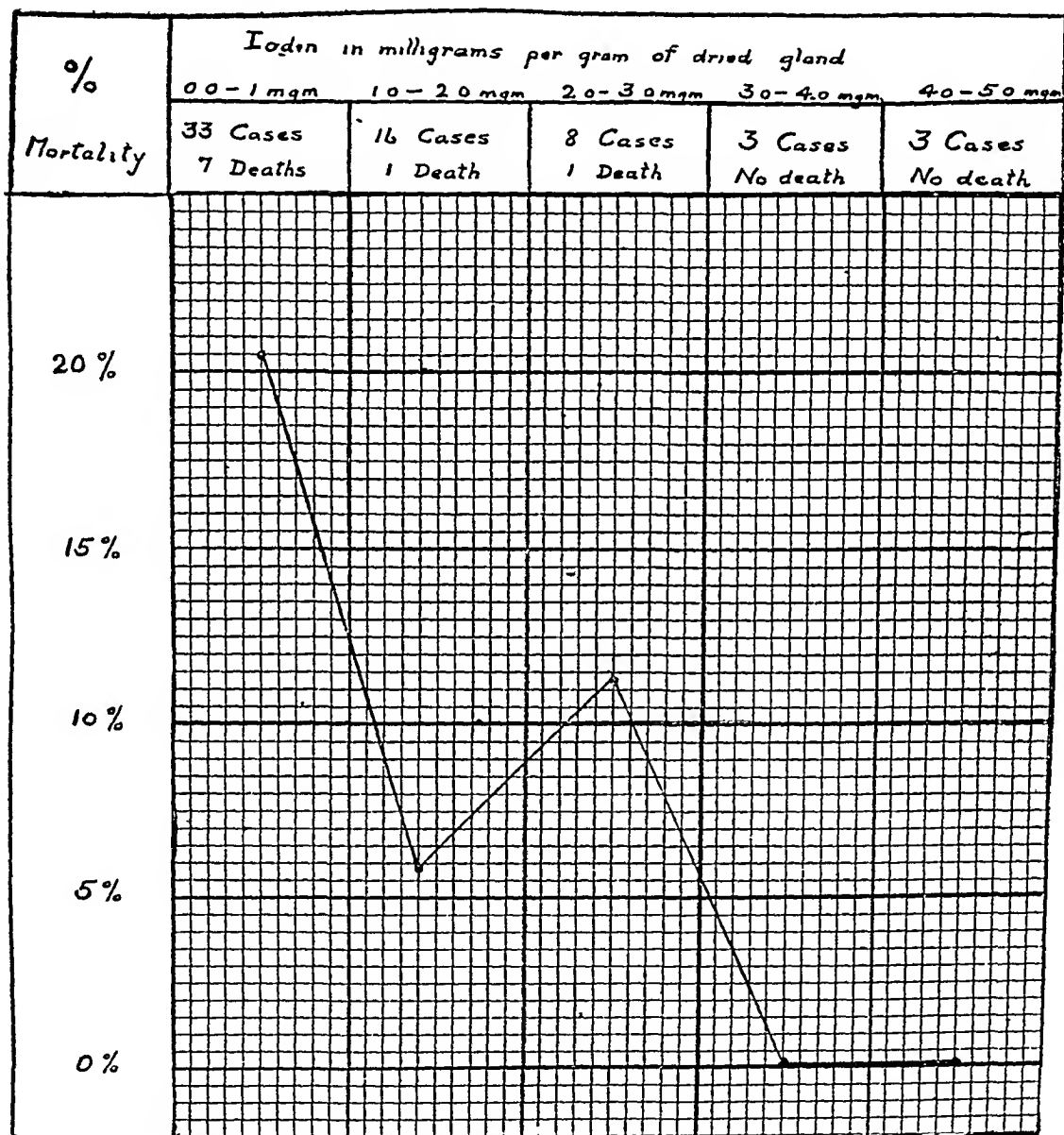


Fig 9—Mortality and iodine content

incident to a fracture of the femur Hirst<sup>59</sup> has collected seventy-one operations other than thyroid in cases of exophthalmic goiter in which the same phenomena of high pulse and temperature were present, of which fifteen terminated fatally Fifth, a comparison of the postoperative rise of

<sup>58</sup> Crile Ohio State Med Jour, 1907, iii, 293

<sup>59</sup> Hirst Am Jour of Obst, 1905, lii, 367

the temperature and pulse in our group of fatal cases with a group of non-fatal cases of similar thyroid and lymphoid changes shows that the manifestations differ only in degree (Figs. 7 and 8)

The second view, that the lymphoid hyperplasia of the thymus, spleen and lymph glands is the cause of death in these cases, has been discussed by Capelle, Caro, Boit and others. Most of the fatal cases, as has been shown by all observers, have lymphoid hyperplasia. The studies of Sawyer, Kochei, van Lier, Carpi and others have shown that this lymphoid hyperplasia, while in no sense specific for the fatal cases or, indeed, for exophthalmic goiter in general, is present to some degree during the progressive stage of true exophthalmic goiter whether ending fatally or not.

The third view, that death is the result of the failure to compensate for some general nutritional disturbance seems the more probable. This failure of compensation is manifested objectively by the series of morphological changes easily demonstrable in the thyroid and lymphoid tissues and which perhaps also exist in other tissues whose objective manifestations of the compensatory reaction are less easily detected. The interpretation of these cell changes as indicative of cell exhaustion is based on the well-known experiments of R. Hertwig and his pupils<sup>60</sup> in producing similar morphological changes in protozoan cells by overwork, overfeeding or starvation, and on the morphological studies in tumor cells by Professor Howard and Dr. Schultz.<sup>61</sup>

The study of the series of changes which take place in a thyroid as it passes from the normal gland through active hyperplasia to the end stage of cretinoid or myxedematoid atrophy, forces us to interpret this process as one of compensation to meet increased functional demands and the failure of this compensation leads to a gradual loss of the finer cell nutrition and, in consequence, of the finer cell function. One cannot say that the general loss of cell energy and of the ability of the body-cells to regulate their function—the two most characteristic features of the disease—are or are not due to a poison. There is, however, no objective evidence that either the thyroid or lymphoid tissue is producing such a poison, but rather the evidence would seem to indicate that if a poison does exist, these tissues are attempting to control it.

### 9 TREATMENT OF EXOPHTHALMIC GOITER

A correct estimation of the value of any plan of treatment is easy or difficult in proportion to the closeness with which the disease follows a type. If the disease is acute and typical, the therapeutic value of any measure is readily determined, but if, on the contrary, the course of the

60 Arch f Protistenk (Suppl.) Festband f R. Hertwig, 1907

61 Schultz Jour Exper Med, Suppl No 1911



disease is chronic and subject to many spontaneous remissions and exacerbations it is extremely difficult to reach a just estimate of the value of any plan of treatment. And when in addition the pathological processes cannot be sharply separated from the physiological, the difficulties opposed to correct judgment are further increased. There is no disease the history of which better demonstrates the truth of these principles than does exophthalmic goiter.

General suggestions covering the recognized facts in the pathology and the physiology of the disease only can be attempted, because in so protean a disease, and in a disease which so markedly tends toward spontaneous recovery, false judgments as to the success or failure of a given measure are unavoidable. The details of application of the general principles to be outlined must be left to the good judgment of the physician and there is perhaps no disease in which the adaptation of the physician's suggestions to the individual case is more important for the obtaining of satisfactory results.

The prevailing modes of treatment have followed closely the prevailing theories as to the causation of the disease. The therapeutic measures at present employed may be divided into two groups, as follows:

- 1 Those directed toward the correction of metabolic disturbances, and in particular the nervous exhaustion.

- 2 Those directed toward reducing or counteracting the thyroid secretion.

Beginning with Group 1, the first requisite is a carefully taken history to ascertain the underlying factors in the central nervous-system exhaustion, whether it can be traced to worry, care, anxiety, fright, overwork, strain, infectious diseases, as typhoid fever, rheumatism or influenza, gastro-intestinal disturbances or any of the many other disturbances with which the symptom-complex may be associated.

Rest, both mental and physical, stands first in importance among all the beneficial measures now at our command. Those who have had the most favorable results with surgical measures have used prolonged rest both before and after operation. As nearly absolute mental rest as possible should be striven for. This may be attempted by a variety of means, but again the physician must adapt his method to suit the tastes, surroundings, means, etc., of the patient. Rarely can one obtain rest at home. More successful is a change of environment, in a hospital or a sanitarium or in the country. In severe cases a rigid Weir Mitchell treatment may be necessary. In milder cases the diversion of a leisurely voyage, or a sojourn at some quiet place by the sea or in the highlands, or a protracted visit with a distant relative or a leisurely-taken camping trip may open up other avenues of mental activity which are as rest-producing to the nervous mechanism as physical rest is to the muscle-cell.

Mental rest frequently has little association with physical rest and we often fall into the error of attempting to obtain mental rest by the same methods that are commonly employed to induce physical rest. The great object to be attained in all cases is to get the patients to a place where they can enjoy quiet, away from their cares, imaginary or real, away from their social duties and their work.

Baths have an important place in the treatment, both for their sedative and their tonic effects. A course of daily baths with carefully graduated temperatures should be instituted. In the severe, maniacal or restless cases the hot bath (100 F) each evening usually ensures sleep and rest. As the patients improve, or in milder cases, the temperature may be graduated downward, thus passing from the sedative to the mildly tonic effect. Perhaps in no case is it wise to reduce the bath temperature below that which is necessary to induce mild vasoconstriction.

**Exercise.** There are three forms: (1) active (voluntary) movements, (2) passive movements and (3) electricity. In all severe cases the muscular weakness precludes attempts at active exercise, but massage should be instituted in connection with the hot baths. In improving or mild cases active exercise as walking, mild gymnastics, etc., should be instituted. These exercises should be graduated so as to avoid fatigue and at the same time to take advantage of the patient's increasing endurance. Electricity has been extensively used, and undoubtedly many of the symptoms have subsided under its use, but the fact that there is no agreement among observers as to the kind or strength of current to use—some recommending the static, others the high frequency, some the galvanic, others the faradic—has led to the conclusion that whatever benefit is obtained is largely due to the mental impression on the patient and the muscular movements induced.

Concerning climate great differences of opinion exist. Some insist on residence in the mountains, others at the seashore. All we know may be summed up by saying that since these patients withstand heat badly, one should avoid the hot, humid climates and seek a cool, dry, pure atmosphere. In patients with cardiac weakness the altitudes may be harmful. In general, mountainous regions of moderate elevation (1,000 to 5,000 feet) are the most favorable and offer less monotony than level surroundings.

**Diet.** Patients often crave unsuitable articles of food, as pickles, spices, pastries, candies, nuts, etc. The food should be plain, well cooked, wholesome, and taken at regular intervals. Stimulants should be avoided. The fact that these patients usually retain good appetites cannot be overlooked when weighing the symptomatology of the disease. It may possibly be interpreted as the organism's attempt to repair the tissue waste. And since tissue waste is one of the manifestations of the disease, we believe

that the diet of these patients should not be curtailed as to proteins, fats or carbohydrates, and that none of the usual articles of food (meats, milk, eggs, butter, sugars, starches, fruits and vegetables) need be restricted except as special indications arise in the individual cases, as for instance glycosuria, diarrhea, vomiting, etc

**Suggestion** The value of suggestion in exophthalmic goiter is universally recognized. The psychical condition of these patients is very unstable. Trivial incidents may encourage them and equally trivial happenings may depress them. It is necessary to acquire the confidence of the patient when time is such an element in the treatment, and only in this way can we expect cooperation. The physician should encourage and cheer the patient. In most cases this can be done without resort to strategy, not to speak of quackery. Hypnotic suggestion should be condemned.

Drugs have little actual value. Speaking of the almost endless list as a whole, their beneficial influence is determined largely by the mental impression on the patient and by the skill and intelligence with which their use is adapted to each particular case. The general hygienic measures instituted at the same time are often underestimated. It should be pointed out that the limits of safety in the use of drugs are very narrow in this disease and drugs should, therefore, be used in small doses and under careful control. The use of drugs is largely symptomatic and may be grouped as follows:

1 The cardiovascular group includes digitalis and its derivatives, strophanthus, convallaria, strychnin, ergot, atropin, veratrum viride, aconite, nitrites, etc. The heart and vessels need neither stimulation nor depression. They need regulation. This regulatory control can be regained but slowly under any condition. Digitalis is the most commonly used. Its use should be confined to such conditions as acute dilatation, valvular lesions or actual myocardial disease. It should not be used for the tachycardia. Rest in bed and the ice-bag are safer and better.

2 For the symptoms of nervousness, restlessness and insomnia a large list of drugs has been used. Among the more prominent drugs are opiates, bromids and coal-tar products. Since the above symptoms are probably due to a loss of, or a weakened inhibitory control over, the body functions, it is not rational therapy to offset this by correspondingly depressing the accelerator mechanisms. The end to be attained is to assist the organism in regaining this regulatory control, and rest in quiet, congenial, comfortable surroundings, warm baths, etc., are more important than drugs. An occasional diam dose of sodium bromid before retiring may be useful if the above measures are impracticable. These patients are peculiarly susceptible to opium and it should not be used. The same is true of the powerful hypnotics and depressants.

3 Iron, arsenic, sodium phosphate and quinin hydriobromate have their advocates. Since the treatment of every case must be carried out on general principles and complications as dyspepsia, diarrhea, constipation, vomiting, anemia, etc., dealt with as they arise, these drugs as well as many others are often of value in individual cases.

4 The use of such animal extracts as thymus, adrenal, ovary, testis, spleen, pituitary or brain tissue is purely empirical and has no known influence. With desiccated thyroid it is different. According to the hyperthyroidization theory it should make the cases worse, while according to the hypo- or dys-thyroidization theory it should produce improvement. The majority of the reports indicate that the drug in small doses makes the patients clinically worse. Nevertheless, there are large numbers of cases in which no noticeable effect has been produced by the drug even in large doses. There are also numerous cases in which definite improvement has followed its use. Several known factors have helped to bring about this lack of uniformity of results. (1) The activity of desiccated thyroid is determined by the iodine in organic combination, and in commercial preparations this is quite variable (the causes for this variation have been discussed in an earlier paper by Marine and Williams<sup>62</sup> and by Hunt and Seidell<sup>63</sup>). (2) The doses used have usually been those arbitrarily established for goiter in general. (3) Clinically, exophthalmic goiter includes a very broad group of cases as regards the duration, prominence, severity and character of the symptoms.

It is certain, however, that desiccated thyroid induces the same anatomical changes in the exophthalmic goiter as in any other developing goiter and that these changes are identical with those produced by iodine, viz., (a) an involution to the colloid state, (b) an increase in the iodine content and (c) a decrease in the blood-supply. In the so-called secondary exophthalmic goiter cases and in cases with manifestations of developing myxedema, doses of from 2 to 5 gr (0.12 to 0.3) daily of the commercial thyroid are often beneficial. In the acute, severe, primary exophthalmic goiter cases this drug should not be employed unless one uses a purified iodothyreoglobulin hypodermatically in doses of  $\frac{1}{50}$  gr (0.002) as recommended by Beebe<sup>64</sup>. On the whole this is a dangerous drug and should be used only in its purified and standardized form in cases under the closest observation. We feel certain, however, that its use in this disease will become more general when the above conditions are fulfilled.

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<sup>62</sup> Marine and Williams. The Relation of Iodine to the Structure of the Thyroid Gland, *THE ARCHIVES INT MED*, 1908, 1, 349.

<sup>63</sup> Hunt and Seidell. Commercial Thyroid Preparations, *Jour Am Med Assn*, 1908, 11, 1385.

<sup>64</sup> Beebe. Treatment of Thyroidism by Specific Serum, *THE ARCHIVES INT MED*, 1908, 11, 315.

5 Iodin has much the same action in exophthalmic goiter with active thyroid hyperplasia as has iodothyreoglobulin, and in addition has the advantage that the dose can be controlled and that the reaction produced depends on the size of the dose and on the existing degree of the thyroid hyperplasia. We have carefully followed the use of iodine in seventeen cases and have not seen any of the injurious effects commonly described.<sup>65</sup> Iodine should be administered by mouth and preferably in the form of the syrup of the iodide of iron, syrup of hydriodic acid or sodium iodide. The initial dose should be small. In extreme cases we have used the syrup of ferrous iodide in doses of 5 minims (0.3 c c) daily for the first week, 5 minims (0.3 c c) twice daily for the second week and 10 minims (0.6 c c) twice daily for the third week. In mild cases the initial dose may be 5 (0.3) or even 10 (0.6 c c) minims twice daily.

Group 2 includes those measures directed toward reducing or counteracting a theoretical hypersecretion. The experimental basis for this theory of the nature of the disease is becoming exceedingly frail.

A. Surgical measures rank first. The more important ones are partial extirpation of the gland, arterial ligation, stretching or excision of the cervical sympathetic, and various combinations of these. It is extremely difficult to arrive at any accurate estimation of the value *per se* of any of these measures. No two observers exercise the same liberality or restriction in making the diagnosis. Successes are more often reported than failures. The general hygienic and nutritional treatment instituted before and continuing for a long time after operations have not been taken into account. Internists generally have used a more rigid standard of cure than have surgeons. The statistics of mortality, improvement and cure based on the total number of cases clinically diagnosed are, for the above reasons, of little value. We have followed a large group of cases from the clinic of Dr. Crile and our findings agree with those of Wilson,<sup>66</sup> Capelle and others that the severity and mortality statistics are more accurately computed from the actual thyroid and lymphoid reactions than from the clinical picture. Indeed, we would go further and state with Crile<sup>67</sup> that it is impossible at present to state accurately the net clinical results of any operative procedure. None of the operative measures or their modifications has been followed by uniform results. As Mackenzie<sup>68</sup> points out, surgical measures most often fail in those cases in which medical treatment most often fails and particularly in those cases which

65 Kocher (*Arch f klin Chir*, 1910, *xvii*, 1166) has recently set forth at length the untoward effects of iodine in exophthalmic goiter. We believe such effects are due to the abuse and not to the physiological use of the drug.

66 Wilson. *Am Jour Med Sc*, 1908, *cxxxv*, 851.

67 Crile. *Post operative Results in Exophthalmic Goiter and Tumors*, Jour Am Med Assn 1909, *liii*, 1675.

68 Mackenzie. *Allbutt's System of Med* 1908, *iv*, pt 1, 383.

theoretically should be most improved. It is impossible to tell whether ligation of one, two or three thyroid arteries will be followed by improvement or not. So also with partial extirpation, improvement may or may not follow removal of one-fourth, one-half or three-fourths of the gland. So also with the sympathetic operation, either stretching or resection may or may not be followed by improvement. Whatever thyroid operation is made, the other factors being constant, the postoperative reaction (so-called hyperthyroidism) and the operative mortality are, in general, proportional to the degree of active thyroid and lymphoid hyperplasia (the anatomical indices of severity). Also many authors have shown that operations on other parts of the body, or injuries, as a fractured leg, or mental shocks, are followed by the temperature and pulse reactions and sometimes death, in proportion to the anatomical severity of the disease.

It is the general experience that a larger percentage of improvement follows in those cases in which some operative measure has been carried out than in those treated medically, but as Bier<sup>69</sup> points out, it is largely subjective during their stay in the hospital and the objective signs clear up only after prolonged treatment. None of the surgical explanations thus far offered for the apparent improvement is free from weighty objections. In our opinion operations should not be undertaken until the thyroid has returned to its colloid or resting state, whether this has occurred spontaneously during general treatment or has been hastened by the action of minute doses of iodine. What has been said refers only to operative measures applied expressly for the relief of the symptoms of the exophthalmic goiter. In each case the general indications for operation, as (1) the relief of mechanical pressure effects, (2) correcting deformity, (3) thyroid tumors and (4) psychic effects, should be considered.

B. The chief non-surgical measures in use to counteract or reduce the hypothetical thyroid hypersecretion are (1) the antithyroid serum of Moebius, (2) the milk of thyroidectomized goats, (3) the thyreolytic serum of Beebe and Rogers, and (4) the Roentgen rays. The hypothetical action of Moebius' serum and of the milk of thyroidectomized goats is one of neutralization. It rests on the assumptions (1) that the serum or milk of thyroidectomized sheep and goats contains an accumulation of substances which the thyroid secretion would normally neutralize and (2) that the gland of exophthalmic goiter is producing an excess of secretion. As with all other remedies some observers report beneficial, others negative results. The prevailing opinions are (von Strumpell, Eulenberg, Erb and Eichhorst<sup>70</sup>) that any improvement occurring during their use is not greater than could be ascribed to rest, hygiene and the passage of time.

69 Bier *Med Kln*, 1908, iv, 16

70 *Med Kln*, 1908, iv, 39

Certainly no specific action has been demonstrated. The theory of action of Beebe and Rogers' serum is that it inhibits the action of the thyroid cells or destroys them. The serum is made by injecting into rabbits or sheep the nucleoproteins of human thyroid. They claim for the serum a high degree of specificity. The work has not been confirmed.<sup>71</sup> Our experience with its therapeutic use is confined to fourteen cases. No improvement could be made out above what normally occurs with rest in bed. We were able to examine the thyroid glands histologically from three of the cases (in two cases during and one about four weeks after treatment) but could not detect any lytic action on the thyroid epithelium.

Roentgen rays have also been used to inhibit or depress the gland's activity. In some cases the gland becomes smaller. No definite thyroid changes are recorded beyond an increase of the capsular and pericapsular fibrous tissues. The value of this form of treatment is still problematical.

### 10 SUMMARY AND CONCLUSIONS

The anatomical changes in the several body tissues in exophthalmic goiter are variable and manifold. The most prominent and most constant change is active hyperplasia of the thyroid and lymphoid tissues. These changes are not constant, since the exophthalmic goiter syndrome, as at present recognized, may coexist with a normal thyroid, with a colloid goiter, with an actively hyperplastic thyroid, with an atrophic thyroid or with a tumor of the thyroid.

The great majority of individuals presenting this syndrome in recognizable form have some degree of active thyroid and lymphoid hyperplasia, and we believe that all true cases with complete clinical syndromes have had, during their developmental stage, active thyroid and lymphoid hyperplasia.

Active thyroid and lymphoid hyperplasia are not specific for this syndrome, since similar anatomical changes are present in a variety of other abnormal body states.

The series of anatomical changes which occur in a thyroid as it passes from its normal or its colloid state through active hyperplasia and on to atrophy or to colloid goiter represents this tissue's biological reaction whenever those biochemical disturbances in the organism's nutrition occur which excite its compensatory activity.

Active thyroid hyperplasia means thyroid insufficiency, and although the causes which excite this activity are unknown and, therefore, may or may not be multiple, still, the basic anatomical reaction of the thyroid tissue seems to be the same in all the several clinical varieties of goiter and, indeed, seems to be the only one with which the thyroid tissue is

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<sup>71</sup> Taylor, A. E. The Treatment of Exophthalmic Goiter with Specific Antiserum, Jour. Am. Med. Assn., 1911, lvi, 263.

endowed The only defined physiological activity of the thyroid secretion is that determined by its iodine content Iodine is related to the exophthalmic goiter thyroid in the same way that iodine is related to the thyroid of other clinical associations and of other animals as well, viz, that iodine varies inversely with the degree of active hyperplasia The ability of the exophthalmic goiter thyroid to take up iodine varies with the degree of active hyperplasia (hence inversely with the amount of iodine present) and is similar to that of other active thyroid hyperplasias in man and the lower animals Iodine induces the same series of anatomical changes in exophthalmic thyroid goiter as in the other varieties of thyroid hyperplasias in man and animals

The temperature and pulse reactions both before and after operation tend to vary with the degree of thyroid and lymphoid hyperplasia The differences between the reactions in cases with normal or with colloid glands and the reactions in cases with marked hyperplasias are too slight for a suggestion of any cause and effect relation The pulse and temperature reactions and the thyroid hyperplasia are parallel and resultant phenomena dependent on more general and more remote causes

An incomplete exophthalmic goiter syndrome may exist with the thyroid normal, or the thyroid may be markedly hyperplastic with the syndrome absent, or, finally, the histological structure and iodine content of the thyroid in a given case of exophthalmic goiter may be reversed without necessarily modifying the symptom-complex

Myxedema does not precede, it occasionally accompanies, but usually supervenes late in the course of exophthalmic goiter and is to be looked on as the end stage of thyroid insufficiency

The immediate postoperative mortality with its associated high temperature and pulse-rate in uncomplicated cases, varies with the degree of active lymphoid and thyroid hyperplasias and is most probably the result of the organism's profound general weakness and exhaustion The degree of active lymphoid and thyroid hyperplasia is therefore the best index of the severity of the disease

The essential physiological disturbance of the thyroid in exophthalmic goiter is insufficiency, its reaction compensatory and its significance symptomatic

NOTE—We wish to acknowledge our indebtedness to Professor G N Stewart for many criticisms and suggestions, and to Professor G W Crile for the use of his surgical material



# THE SYMPTOMATOLOGY OF TEMPOROSPHEOIDAL TUMORS<sup>2</sup>

FOSTER KENNEDY, M D, B CH (QUEEN'S) -  
NEW YORK

## INTRODUCTION

In a paper on the "Localization of Intracranial Tumors," Byrom Bramwell<sup>1</sup> has stated that in two cases reported by him in which the tumor involved the temporosphenoidal lobe, there were, practically speaking, no localizing symptoms

I have been in the habit of regarding the temporosphenoidal lobe as, par excellence, *the* silent area of the brain. In the relative order with which they can be most easily and certainly diagnosed I would place tumors in the following situations (1 and 2) pons Varoli and medulla oblongata, (3) centrum ovale (cases in which the optic radiations of Gratiolet are directly implicated), (4) tumors of the occipital lobe, involving the half-vision center or the optic radiations, (5) tumors of the motor area, in which the tumor produces irritation and gives rise to localized epileptiform convulsions, (6) tumors of the cerebellum, (7) tumors of the frontal lobe, (8) tumors of the upper part of the parietal lobe, *and last of all, the most difficult to diagnose and locate*, (9) *tumors of the temporosphenoidal lobe* and especially, of course, tumors of the right temporosphenoidal lobe

That the words which I have underlined represent an opinion very generally held is evident, when we find that writers of the eminence of Beevor<sup>2</sup> and Mills<sup>3</sup> have also in recent years laid stress on the great difficulty in the diagnosis of tumors involving the cerebral area below the Sylvian fissure

As an example of this difficulty may be mentioned the case reported by Alexander Bruce,<sup>4</sup> which, notwithstanding the presence of intense headache, right facial weakness and marked disability in speech, was diagnosed as "hysteria," but which on autopsy was found to have a tumor the size of a hen's egg in the anterior third of the left temporosphenoidal lobe

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\*The author wishes to express his thanks and his great indebtedness to the members of the medical and surgical staff of the National Hospital, London, for their permission to make use of the material on which this paper is based

1 Bramwell, Byrom Localization of Intracranial Tumors, Brain, 1899, *vol.* 11, 37

2 Beevor Localization of Cerebral Tumors, Lettsom Lecture, Lancet, 1907, *vol.* 1, 495

3 Mills Tumors of the Cerebrum, 1906 p 36

4 Bruce Tr Med-Chir Soc, Edinburgh, 1882, *vol.* 11, 94

The consensus of authoritative opinion seems then to characterize the temporo-sphenoidal lobes as by far the most latent area of the brain. They are vast regions practically uncharted, for in them experimental physiology has been able to assign definite functions to but comparatively small portions. Again, temporo-sphenoidal tumors are relatively rare, and observers have only exceptionally been able to study more than single isolated cases. Hence, a systematic examination of the symptomatology of this condition has hitherto been impossible.

During my residence at the National Hospital for the Paralyzed and Epileptic, I had opportunities for repeated examinations of a large number of such cases.

In some, in which the symptoms were clear and the diagnosis certain, the patients, for various reasons, were discharged from the hospital without operation, in others, death supervened and permission for autopsy was refused, in others, again, the growth was found to involve not only the temporal but also the frontal, or parietal or occipital regions, thus possibly introducing doubt as to the causation of the symptoms.

For the purposes of this paper all such cases have been neglected, and only those nine in which the lesion was proved to be confined to the temporal lobes will be reviewed. By thus rigorously confining my attention to indubitable cases of temporo-sphenoidal tumor, I hope convincingly to demonstrate, first, that such tumors present a definite and uniform symptom-complex, pathognomonic of tumors in this region and in this region alone, and, second, that not only can they with certainty be diagnosed, but that it is still further possible clinically to distinguish those in the right hemisphere from those in the left.

It must be remembered that an intracranial tumor is not merely a localized lesion affecting centers in its immediate vicinity alone, but it also acts as a foreign body growing in a non-distensible space and producing in a definite and almost invariable sequence, compression of centers more or less remote.

The symptoms-complex to be put forward later as characteristic of tumors in the right and in the left temporal lobes, are the result of systematic examinations of patients with especial regard to the effects of irritation or destruction of centers proved experimentally to be situated in these areas, and also to the results of compression in all directions on adjacent structures, as will be shown, the success attendant on the subsequent surgical procedures has been considerable.

It may be said that the greater the latency of a brain area, the greater the difficulty in the diagnosis of damage to that area, but also, if accessibility be granted, the more safely can one operate on that area.

The value of the removal of any intracranial growth as regards the restoration of normal health to the patient must depend largely on the

degree of latency of the brain tissue affected, and the ability of the patient to carry on a useful or comfortable existence without the aid of that brain area, the removal of a left-sided subcortical fronto-parietal growth resulting, perhaps, in complete right hemiplegia and motor aphasia, is an enterprise not lightly to be undertaken, nor is a tumor in one of the pontine angles in a much more favorable position, in spite of the power of the unaffected lobe of the cerebellum to effect more or less compensation for the destruction of its fellow, but in the right temporo-sphenoidal lobe we have a region comparatively latent and eminently accessible

#### THE LOCALIZATION OF THE CENTERS FOR HEARING

By extirpation of the posterior divisions of the three external temporal convolutions of each hemisphere, Munk<sup>5</sup> was able to produce complete deafness in dogs by varying the area of cortex removed, he believed that he could distinguish separate centers concerned with "cortical" and "psychic" hearing, and also with the exact appreciation of pitch, the higher tones apparently were perceived in the anterior, and the lower in the posterior parts of these convolutions

His views were not endorsed by Ferrier,<sup>6</sup> whose experiments showed that in monkeys complete deafness followed the cauterization of the superior temporal convolutions on both sides of the brain

The effect of stimulating the superior temporal convolution of one side was found by Ferrier,<sup>6</sup> Hitzig<sup>7</sup> and Goltz<sup>7</sup> to consist in a pricking of the opposite ear, wide opening of the eyes, dilatation of the pupils and turning the head and eyes to the opposite side all the secondary phenomena of audition

On the other hand, Schafer,<sup>8</sup> repeating Ferrier's experiments, was unable to obtain the same results

Campbell<sup>9</sup> found that the temporal convolutions known as the transverse gyrus of Heschl differ from all other parts of the temporal lobe in the histological structure of their fibers, which are corticopetal and evidently represent the uppermost link in the chain of auditory neurones

Having reviewed the functions of the analogues of these fibers in the visual area, Campbell<sup>10</sup> suggests that the transverse temporal gyrus represent the primary center for the reception of auditory stimuli, it follows that ablation of these convolutions from both hemispheres would result

5 Munk Ueber die Funktionen der Grosshirnrinde, 1890, p 31

6 Ferrier Functions of the Brain, 1886, p 305

7 Hitzig and Goltz Quoted by Lewandowsky in Die Funktionen des zentralen Nervensystems, Berlin, 1907

8 Schafer Brain, 1888, xi, 143

9 Campbell Histological Studies on the Localization of Cerebral Function, 1905, p 169

10 Campbell Histological Studies , 1905, p 161

in total deafness, and there are reasons for believing that the discrepancy between the results of Ferrier's and Schafer's experiments may have an explanation in the failure of the latter to remove these transverse convolutions

To summarize this greatly curtailed account, it may be said that the consensus of opinion—experimental, clinico-pathological, and anatomical—is in favor of the centers for hearing being situated in the transverse temporal gyrus of Heschl and the posterior three-fifths of the superior temporal convolutions

#### THE LOCALIZATION OF THE CENTERS FOR SMELL AND TASTE

Broca<sup>11</sup> in 1879, and Zuckerkandl<sup>12</sup> some years later, demonstrated that in animals with a highly developed sense of smell, there is a corresponding enlargement in the lobus pyriformis, which forms a large part of the hippocampal convolution; it was also shown that the size of the pyriform lobule is greatly reduced in anosmatic animals, and degeneration has been found in this same area after division of the olfactory bulb of the same side

The presence or absence of the olfactory sense in the lower animals is difficult to determine, but Ferrier<sup>13</sup> found that electrical irritation of the hippocampal lobule in the monkey, cat, dog, and rabbit, was followed by the same reaction in all—a peculiar torsion of the lip and nostril, particularly of the same side, and ablation of this region was followed by a loss of perception of odors and tastes

Clinicopathological evidence in the main confirms Ferrier's view that the olfactory and probably gustatory centers are situated in the hippocampal lobule, while Hill's<sup>14</sup> observation that the gyrus dentatus of the cornu ammonis is the only structure wholly wanting in the anosmatic brain, tends more accurately to define this localization

#### SYMPTOMATOLOGY

The various phenomena of intracranial tumors are usually separated into those produced by general pressure, and those produced by focal disturbance in the neighborhood of the growth. This division is one which many times has been shown to be not only unscientific but also clinically fallacious. In the description of a series of cases having many points in common, however, it is convenient, and solely for this reason is it here retained

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11 Broca, P. Localisations cérébrales, recherches sur les centres olfactifs, *Rev d'anthrop*, Paris, 1879, II, 390

12 Zuckerkandl. Ueber das Riechcentrum, Stuttgart, 1887

13 Ferrier. Functions of the Brain, p 316

14 Hill. The Hippocampus, *Phil Tr Roy Soc London*, 1893, clxxxiv

A detailed examination of the symptomatology of the nine cases under review will enable us to ascertain the characteristic effects of tumor growth in the temporo-sphenoidal lobes, and later to differentiate those on the right (Cases 1, 2, 3, 4) from those on the left (Cases 5, 6, 7, 8, 9)

Signs and symptoms of general intracranial pressure

### *Headache*

Headache was present in all. It was rarely constant. It occurred at irregular and often at long intervals, and was usually spoken of as coming in bouts or attacks synchronous in many cases with nausea and vomiting. In only one respect, however, was it of uniform character—as regards localizing value it was little more than useless. In no instance was the pain referred to the temporal region, and only in Cases 1, 4 and 5, was it more frequently felt on the same side as the tumor. In two cases the headache was occipital, in five frontal, and in two it was referred to both the frontal and occipital regions.

It is impossible from a series of nine cases of tumor affecting a single brain area to draw conclusions applicable to other intracranial growths, but it is essential here to emphasize that not in a single instance was the headache of these temporo-sphenoidal cases referred to the regions of the tumor site. Neither was there in any case localized cranial tenderness.

### *Vomiting*

Vomiting occurred with variable frequency in each of the nine cases, two patients suffered from single attacks of short duration, three had bouts at intervals of several months, and four were subject to attacks at frequent but irregular periods. In all, nausea alone often occurred, and it invariably accompanied the vomiting which in no sense presented features distinguishing it from that of gastric origin; thus, it did not conform to the "projectile type," which by many is erroneously considered to be the essential characteristic of the vomiting of cases of intracranial growth. In four of these cases, nausea and vomiting were particularly associated with subjective unpleasant sensations of taste and smell, and, it might be argued that these features tended to prevent the appearance of the vomiting of classical type, but, broadly speaking, the condition found in this series, is identical with that which occurs in most cases of tumor situated above the tentorium cerebelli.

### *Papilledema*

Leslie Paton<sup>15</sup> recently brought forward statistical evidence to show the impossibility of reaching trustworthy conclusions as to the site of a tumor in the cranial cavity from the greater degree of edema in one or

<sup>15</sup> Paton, Leslie. *The Ophth Soc U Kingdom*, 1908, LVIII, 112

other of the optic disks. This iconoclastic opinion was at the time emphatically opposed by Sir Victor Horsley and Sir William Gowers, and their view has lately been endorsed by Risien Russell<sup>16</sup>

Hence it may be of interest to ascertain what diagnostic value this sign possessed in the present series. Bilateral papilledema was present in eight of my nine cases when first they came under observation, in the other, the condition developed within ten days of admission in the eye ipsilateral with the neoplasm, and was found in the contralateral eye also some three or four days later.

In one case (No 2) the condition was subsiding into atrophy in both eyes, especially the right, but in the remaining eight the type of papilledema was that usually associated with rapid onset and severe intracranial pressure. Careful measurements of the degree of the swelling of the disks were taken in seven cases and were found to vary between three and ten diopters, the greater swelling was ipsilateral with the tumor in five cases and contralateral in one, in the last the edema was equal on either side. It must be again pointed out, with reference to the interpretation of these figures, that the only case in which a greater degree of swelling was found on the side contralateral to the tumor was also the only case in which the pathological process was in a retrograde condition, and that, accordingly, the true meaning of the appearances was that the ipsilateral edema was of earlier origin than the contralateral, had advanced further, and at the time of observation had more nearly completed its life-history: that this is the explanation of the condition will be at once apparent when it is added that in the ipsilateral eye there was much old exudate, whereas in the contralateral there was none, that the retinal arteries were much more diminished in size in the ipsilateral eye, and that the acuity of vision in each eye was in direct proportion to the degree of arterial change.

Sir Victor Horsley<sup>17</sup> has many times pointed out the error of estimating the severity of papilledema by the height of the disk swelling alone and has demonstrated the absolute necessity of considering as one complete picture all the appearances shown by ophthalmoscopic examination before accurate conclusions are to be attained.

It is convenient here to group retinal hemorrhages, retinal striations and the phenomena known as macular figures under the heading of "exudates," and it is generally agreed that in the majority of cases the presence or absence of such exudates assists an observer to an opinion on the severity of the condition.<sup>18</sup>

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16 Russell, Risien. *The Cerebellum and Its Affections*, Lettsom Lecture, *Brit Med Jour*, 1910, p 497.

17 Horsley, Sir Victor. *Brit Med Jour*, 1910.

18 Gunn, Marcus. *Brit Med Jour*, 1907, p 1126.

Six of these cases had more exudate on the fundus oculi ipsilateral with the tumor, one had more on the contralateral fundus, and in two cases the amount seemed identical on the two sides. The result of craniectomy on the condition of the optic disks was remarkable, six patients were discharged from the hospital, from four of whom a tumor had been removed. In two of these papilledema had disappeared a month after the operation and in each of the other two it had subsided by four diopters, this result was associated in every case with marked improvement in visual acuity.

In the two cases in which the tumor was seen but not removed papilledema completely disappeared.

Leslie Paton and others have spoken of the frequency with which patients suffering from papilledema complain of transient amblyopia. Seven of my patients complained of this symptom and spoke of it as having been productive of very considerable distress.

Bordley and Cushing<sup>19</sup> in a recent communication have advanced the suggestion that in cases of heightened intracranial pressure there is a marked diminution in color perception, and in cases in which there obtains gradually increasing pressure on an optic tract it has been long recognized that in the earlier stages of the disease there may be complete color-blindness in the opposite visual field, with retention of all other forms of visual perception.<sup>20</sup> An examination of the pathological findings in my patients suggests the probability of hemianopia or hemiachromatopsia having been present during life owing to the proximity of the growth to the optic tract and radiations. In all cases the existence of hemianopic defect was considered and negatived as the result of examination.

Five patients were examined perimetrically for various colors, the sole abnormality discovered was the concentric contraction of the visual field so often associated with severe, and especially with protracted, papilledema.

### *Fits*

Under this generic title I shall describe the several varieties of psychical and physical phenomena arising presumably as the result of irritation of cerebral centers by tumor growth in the temporosphenoidal lobes.

It seems most convenient as a preliminary measure to divide these into *major*—those attacks in which consciousness was lost—and *minor*—those in which consciousness was retained though in some cases transformed.

19 Bordley and Cushing, H. Arch. Ophth., 1909, xxxviii, 451.

20 Swanzy, Sir Henry. Oliver and Norris' Diseases of the Eye, N. 11, 552.

All but two patients of my series (Cases 3 and 6) suffered at some time or other from sudden attacks of loss of consciousness, associated with cyanosis, stertorous respirations and in four cases generalized convulsions were also present, with tongue-biting and sphincter relaxation.

These seizures, in themselves, present little to distinguish them from those commonly seen in patients suffering from epilepsy of so-called idiopathic origin, but it is to be noticed that in all, a warning or "aura" of some kind was present, and in all, some disability either in speech or in the motor and sensory systems followed the attack. Patient 2, who had her only major attack in the hospital was found to have a condition of reflexes after the fit had passed, signifying that a greater stress had fallen on the right hemisphere than on the left—the left abdominal and epigastric reflexes being abolished, while the others were but slightly diminished—and the left plantar reflex being of extensor type in contrast to a flexor response on the right side.

In two other cases (1 and 5) there was a history of postepileptic weakness in the limbs contralateral to the tumor, and patients 5, 6, 7, 8 gave an account of transient difficulty in speaking after each attack, the nature of this will be dealt with later.

Those attacks which were not associated with definite loss of consciousness were of so varied a nature as to demand examination in detail.

Dr Hughlings Jackson<sup>21</sup> was the first to draw attention to a type of epilepsy in which the general attack was associated with subjective sensations of taste and smell. These, he considered, were due to irritation of the anterior poles of one or other temporosphenoidal lobe, where Dr Ferrier by experiment had succeeded in localizing the centers for these senses. Following the clue given him by Ferrier's experiments, he called such seizures "uncinate fits," and later was able to prove the correctness of his hypothesis by the examination of the brains of persons who, during life, had been subject to epilepsy of this description.

Sander,<sup>22</sup> Lockemann,<sup>23</sup> Westphal<sup>24</sup> and Schlager<sup>25</sup> all reported cases of general epilepsy preceded by subjective sensations of smell, in which tumors were found involving the frontal and temporal lobes, in all of these early cases, however, the olfactory bulbs or tracts were affected together with the hippocampal gyri, and from them no precise conclusion could accordingly be reached regarding the functions of the last-named convolutions.

21 Jackson, Hughlings *Med Times and Gaz*, 1876

22 Sander, Wilh. *Epileptische Anfälle mit subjektiven Geruchsempfindungen* etc, *Arch f Psychiat*, 1873-1874, iv, 234

23 Lockemann *Ztschr f ration Med*, vii, 340

24 Westphal *Allg Ztschr f Psychiat*, vii, 485

25 Schlager, Ludw. *Ztschr d Gesellsch d Aerzte zu Wien*, 1858



In 1882, however, McLane Hamilton<sup>26</sup> of New York published a case of a woman who had sustained a head injury in childhood and afterward was subject to sudden attacks "of disagreeable odor, sometimes of smoke, sometimes of a fetid character, which rose in her head and choked her"—an experience almost invariably followed by general epilepsy. She died of phthisis two years after coming under observation, and was found to have a hemorrhagic pachymeningitis localized to the anterior and inferior part of the right temporosphenoidal lobe. The olfactory bulbs and nerves were unaffected.

In 1886 Anderson<sup>27</sup> reported a case of pituitary tumor involving the left temporosphenoidal lobe in which during life there had been paroxysmal attacks of "a rough, bitter sensation in the mouth" with chewing, spitting movements and other phenomena to which reference will be made later.

Dr Jackson<sup>28</sup> also drew attention to peculiar, transient, psychic variations of somewhat elaborate character occurring as an expression of unstable nervous control, and often heralding or replacing a severe epileptic convulsion.

Complex intellectual states occurring as the initial stage of "grand mal" were alluded to by Herpin<sup>29</sup> in 1867, who reported the following case:

Une jeune personne d'un esprit très observateur racontait ainsi le début de ses attaques: "Je suis prise, sans cause, d'une tristesse subite, et à l'instant même mes yeux restent fixés sur un objet et ma pensée sur une idée qui me rappelle l'image très-nette d'un ancien rêve, l'idée fixe m'absorbe tellement que, quoique je regarde toujours vers le même point, je ne vois plus d'objet."

This "voluminous mental state" as described by Dr Jackson was often associated with those crude sensations of taste or smell which have been mentioned above as being due to irritation of the uncinate gyri, and masticatory movements have been frequently observed suggestive of a discharging lesion in the neighborhood of the gustatory centers. As a third association with dreamy states may be cited an epigastric sensation, invariably unpleasant and often accompanied by a feeling of intense fear.

It is not claimed that these incoordinated resuscitations of sensory impressions, now known as dreamy states, can occur only as the result of gross irritation of the temporosphenoidal lobes, but rather that in

26 Hamilton McLane. On Cortical Sensory Discharging Lesions, New York Med Jour, 1882, xlv, 582.

27 Anderson, James. Sensory Epilepsy, Brain, 1886, ix.

28 Jackson, Hughlings. On a Particular Variety of Epilepsy, etc., Brain, 1888-1889, xi, 179.

29 Herpin. Des accès incomplets d'épilepsie, 1867, quoted by H. Jackson.

those cases in which they occurred, and organic intracranial disease was later found to be present, the lesion has invariably been found to be situated in the temporal lobes

That they may occur in persons who are to all outward appearance in perfect health is patent when one considers how many references to them are scattered through the entire body of English literature, nor need inquiry among apparently normal individuals be far extended before a "subject" be discovered

Descriptions of dreamy states show extraordinary variations, possibly dependent on the severity of the attack, on the causative factor of the attack, and certainly to a great extent on the power of the patient accurately to observe his experiences, and later to clothe them in language sufficiently concrete to be intelligible

The dreamy state is seldom associated with actual loss, but rather with an alteration of consciousness, the patient suddenly becomes aware of everything being changed, yet very familiar, a feeling of reminiscence, as though everything had happened before, so long ago that measurements of time are transcended, the feeling of old-time familiarity is so acute that it seems as though it *must* be that he *surely* knows what is about to happen, what the next word in the conversation will be, what the next movement of his companion will bring about. The sense of prescience is so acute as to give mental pain because of its inevitable unfulfilment, he stands for an instant on the very edge of the "unknowable"—the veil is about to be torn away—and then, as suddenly as it came, the elevation of consciousness is gone and the commonplace returns. That the condition is not of the nature of a memory is apparent on questioning the more intelligent of those who experience it, it is not even a memory half-grasped but still elusive—that, at least, is tangible though evasive, it is of ordinary experience and subject in the greater part to conscious control, but *this* is beyond all things, beyond thought or wish, and beyond language to portray

It has been said<sup>30</sup> that attacks such as these are not found in the uneducated or in persons incapable of entertaining abstract ideas, but is it not more probable that subjects of lower mental development are unable lucidly to narrate psychical phenomena of such varied and nebulous character as tax to the utmost the descriptive powers of some of the greatest masters of the English tongue?

Tennyson says

As when with downcast eyes we muse and brood,  
And ebb into a former life, or seem  
To lapse far back in some confused dream,  
To states of mystical similitude,

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30 Crichton Browne, Sir, James Cavendish Lecture, Dreamy Mental States, 1895, p. 7

And again in "The Two Voices"

Moreover, something is or seems,  
That touches me with mystic gleams,  
Like glimpses of forgotten dreams—

Of something felt, like something here,  
Of something done, I know not where,  
Such as no language may declare

Where defeat is almost acknowledged by such a singer, how can we expect mute and inglorious patients to succeed!

Of the present series, seven patients gave an account of attacks of "coming over dreamy," during which they looked "dazed and lost," but only two, both of whom were exceptionally intelligent, were able much further to elaborate their descriptions

The type of dreamy state which I have attempted to describe is probably the least complex of those which are found associated with gross intracranial disease, in a considerable number the imitation of the higher mental centers produces, not merely "a peculiar thought" as a man under Dr Coats<sup>31</sup> observation expressed it, but a subjective projection of that thought, so that before the patient there appears, as it were, a mirage or, more commonly, spectral faces

It may be said, however, that certain elements—defective objective, and increased subjective consciousness, and a sense of reminiscence, run through all these primitive forms of mentality like the theme in an opera

It is well-nigh impossible to classify the various modifications of dreamy states which were present in these cases indeed, the terms in which several of the patients described their attacks were so vague that no paraphrase could successfully convey their meaning

For over twenty years my first patient had had epileptic fits of ordinary character and without auriæ, at intervals of three to six months. In May, 1907, while dressing, she suddenly heard a bell ringing, then saw a "strange bad woman" clad in rags, and smelt a most evil odor which originated, she thought, in the stranger's clothes, she felt terribly afraid "as though some awful thing were about to happen", nausea was present and she complained of pain around the heart, and in the pit of the stomach, and tingling throughout the inner aspect of the left upper limb. For some seconds she seemed dazed and frightened, then screamed, became suddenly unconscious and passed through all the stages of a severe epileptic attack which in no way differed from her previous fits

While in the hospital she had several such attacks in which, however, the sensation of dread was often the first warning of the onset of

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31 Coats Brit Med Jour 1876, 11

a fit, and in the stress of this emotion her facial expression invariably was that of one "facing an expected horror"<sup>32</sup> (compare Case 2)

The psychical projection in this case, in its elaboration and the constancy of its recurrence, resembled that of a patient of Dr Hughlings Jackson and Dr Beevor,<sup>33</sup> in which, however, the vision of the "little black woman engaged in cooking" was not associated with any sensation of terror, but on the contrary was rather agreeable than otherwise

Neither of these patients was deceived as to the unsubstantial nature of her visitor, nor among other cases I have seen or read of was there one in which the patient doubted the subjective nature of the phenomenon. An important feature of V F's attacks was the occurrence of tingling in the left arm and hand, due to "spread" of excitation to the post-Rolandic cortex—theoretically a probable and frequent event but in reality of rare occurrence as a result of tumor growth in the temporo-sphenoidal lobes. Anderson's patient,<sup>27</sup> to whose case reference has already been made, had attacks in which there was a combination of crude subjective sensations of taste with dreamy reminiscences of considerable complexity, prefaced by a "peculiar sensation" in the arm and hand contralateral to the tumor

It is necessary now to consider the experiences of my second patient—a schoolmistress and an exceptionally intelligent woman. She was admitted in July, 1907, complaining that for two years she had been subject to "nervous attacks" sudden, inexplicable shocks associated with an indescribable feeling of terror and apprehension, which would pass off in a minute or two and leave me weak and trembling." There was no loss of consciousness. These sensations were apparently causeless, and occurred several times daily quite independently of what she might be doing at the moment

Her general health was unaffected. From January, 1907, she could distinguish two types of seizure

1. Major attacks occurred daily, beginning with "an overpowering sensation as if I am going into a sound slumber" a kind of dreaminess, I feel prostrate. I know where I am, but my feelings seem unreal a far away unearthly feeling. I know that I am myself all the time, neither I myself nor the things around me are changed, but the relationship between myself and them is altered. I do not think I can speak in these attacks. I was in one when Sister came round a little while ago. I knew she was near, but I could not take the medicine, I could not explain to her why I could not take it. I do not think I can move in these attacks.

"Sometimes there is a kind of buzzing, whirling sound, which seems unreal though not far off. I do not take any interest in things, though I am aware of them. I always try to find out what the attack is like, I am sufficiently con-

32 Jackson, Hughlings and Stewart Purves. Case of Tumor in the Right Temporosphenoidal Lobe, Brain, 1899

33 Jackson and Beevor. Brain, 1889-1890, vii, 358

scious to try to remember what I am experiencing in order to tell the doctors about it. Nearly always there is a terrible sensation of fear, I am aware there is nothing to be afraid of, but the feeling of pure fear is as bad and horrible as it was at first" [a reference to the attacks originating eighteen months before]

"This fear is not associated with any object or person whatever—I *know* everything is all right but, nevertheless, this dread [of nothing] persists during practically the whole of the attack"

She had no visual phenomena, and she had neither defective orientation of her limbs nor feelings of transference of herself in time or space. Neither was there any sense of disturbance of the size of herself or parts of herself. (Anderson's patient had a sensation of "swelling" in the hand contralateral to the tumor.) "My children always know when I am going to have an attack because of the movement of my face, they tell me I make champing, sucking movements and twist my mouth about"

These attacks were not essentially associated with sensations of difficulty in breathing or with any cardiac sensations, which were more often present in what she called

2 Minor attacks occurred ten or twelve times a day. They varied much. "It's a sudden feeling of hopeless despair, though I'm naturally always in good spirits. I know there is nothing to be despondent about. It's not in relation to any of my thoughts or ideas. I do not despair *about* anything, but it's just as hard to bear for the time being"

"Other unhappy, uncomfortable sensations may constitute the attack, which I can't find adjectives to express. I want to know what they are all about. They seem so strange, and without cause. These sensations never seem to be real. even when I am feeling them. I know they have no cause, but I can't throw them off"

In August, 1907, this patient for the first time began to have frequent subjective sensations of smell

"It comes several times a day, and bears no relationship whatever to my other attacks. I am quite certain of this. It often lasts as long as ten minutes, it seems to be in the ward round about (never in the nostrils), it seems to come from somewhere on my right, what makes me think it is my own creation is that I know I don't really smell anything"

"This smell is neither pleasant nor unpleasant, it is not of the nature of a scent nor a perfume but rather like something in a factory or a brewery, it is quite unfamiliar. I have never smelt anything like it before"

She never had any subjective sensations of taste

On Oct 16, 1907, she was sitting up in bed writing a letter, when she suddenly felt "a strange sensation of dread of being overpowered overwhelmed"

"At the same time I felt my neighbors must have known what was wrong with me, that they must be looking at me. I seemed almost to know what was passing in their minds about me just as if there must have been some 'wireless telegraph' between myself and them. Then things seemed different as though I were somewhere else. There were a lot of loud voices. I don't remember any more"

She then uttered a shrill cry and fell backwards and to the right she became cyanosed and breathed stertorously. The left side of her face was contorted, the upper extremities were adducted and semiflexed at the elbows, the hands were tightly clenched. This rigidity was maintained for a few seconds and succeeded for some ten seconds more by slight jerking movements of all four limbs.

Five minutes after the return of the corneal reflexes, she was found to have marked weakness in the left side of the face, of supra nuclear type, exaggeration of the deep reflexes on the left side, abolition of the left abdominal and epigastric reflexes, while the plantar response of the same side was definitely of the extensor type. The reflexes of the right side were normal in all respects.

Reference may now be made to the five remaining patients of my series who complained of sensations analogous to those I have just described.

Patient 3 never complained of "attacks" at any time, he spoke of frequently hearing "a sound like singing," which, however, he was unable to describe in any further detail.

Patient 4, for three months previous to admission to the hospital, was subject to "sudden attacks of faintness and dreaminess" during which—according to his wife—"he looked dazed, and had a far-away look in his eyes."

These fits were frequently accompanied by a "sudden taste in the mouth—like ink," and a sensation of smell, which he never described but always complained of.

He was under observation for but three days, during which he was evidently suffering from very severe general intracranial pressure with consequent mental impairment, further details of his seizures were therefore not obtainable.

Patient 5 was subject to "sudden attacks of strangeness . . . I get a swimming in the head, not a dizziness exactly . . . I feel dreamy . . . but I don't lose myself," i. e., he did not lose consciousness. This patient never had subjective sensations of any special sense.

Patient 6 had had attacks since May, 1907, in which he "looked dazed and lost." He did not lose consciousness in these seizures, but while they were in progress he became completely unable to recognize his surroundings or to tell where he was—and although he had been a sailor for many years he was without power to distinguish the points of the compass as long as this curious mental state persisted. He never suffered from loss of consciousness nor convulsions, nor had he at any time any crude sensations of smell and taste.

Almost completely analogous to the condition of this patient is that of one reported by Sir James Crichton-Browne,<sup>34</sup> who "in youth and manhood was distressed by brief seizures which may be described as loss of orientation, but which he himself nicknamed "a topographical topsyturvy" Generally, when out walking and alone, his consciousness of his geographical bearings became momentarily confused, and this without vertigo or apparent movement of objects from side to side

Patient 7, for three months before coming under observation, had suffered from frequent subjective sensations of taste and smell, "like a vapor in the mouth                      like the smell of smoke                      the smoke of a foul pipe                      coarse tobacco" This sensation prefaced three attacks of loss of consciousness and generalized convulsions, but also frequently occurred alone The patient had no dreamy states

Patient 8 was a woman who had had, as was found at the operation, long-standing ventricular distention, in addition to suffering from a considerable degree of aphasia, she was mentally inarticulate For seven years she had been subject to attacks of major epilepsy, prefaced by "a horrid smell of rotten fish," and followed by transient difficulty in speech In addition to these more serious manifestations she had frequent sudden attacks "of coming over dreamy," which may have been the result of increased intracranial pressure but which, in so far as each was invariably preceded by an olfactory aura, were in all probability produced by a discharging lesion in the region of the uncinate gyrus of one or other side, spreading to the adjacent temporo-sphenoidal convolutions

This patient had many such seizures when under observation, she would suddenly exclaim, "Oh, the smell," make smacking and spitting movements with the lips and gestures of disgust and repulsion Her face would become pale and anxious, and her eyes fixed on some far-distant point She usually answered if spoken to, but in a low colorless voice, consciousness was never lost and the reflexes remained unchanged The duration of such seizures was usually about two minutes

During the five months previous to admission to the hospital, Patient 9 complained of "an almost constant horrible taste in the mouth" For the same period she was subject to momentary losses of consciousness, with frequent sudden lapses of memory for the names of familiar objects, she had no dreamy states

### *Speech Defects*

From cases of neoplasms producing functional depression or destruction not only of sharply limited and contiguous zones of brain tissue, but also of areas situated at distances varying directly with the size of the tumor, the rate of its growth, and the degree of ventricular distention

34 Crichton-Browne, Sir James *Dreamy Mental States*, p 16

it has created, it is impossible to procure precise data of the cerebral localization of the several attributes of speech

Such data have been acquired by the study of the effects of experimental lesions, and by the investigation of cases in which the lesions were of sudden origin, of definite limitation, and decisively destructive in their results

The effects of tumor formation in or near centers concerned in speech, thus localized, differ materially from those produced by vascular lesions in the same situation, and consist, at least in the earlier stages of the disease, in deterioration rather than in abolition of function of the centers and their annexes

We are now more immediately concerned with the auditory center, which, as has been shown above, is probably situated in the transverse temporal gyrus of Heschl and the posterior three-fifths of the superior temporosphenoidal convolution. The subdivision of this center into one area immediately concerned with the appreciation of ordinary and of musical sounds, and another, reserved for the interpretation of heard speech, may for our present purpose be neglected, inasmuch as the size of the lesion in these cases precludes the possibility of such minute differentiation

The center for heard speech is almost certainly situated in the left hemisphere in right-handed persons, in nearly all cases of sensory aphasia occurring as the result of injury to the right temporosphenoidal lobe, some anomalous circumstance has been discovered to account for the condition. It was found by Oppenheim<sup>35</sup> in two cases of affection of the right temporal convolutions that in one, there was acquired left-handedness in a woman aged 59, who had been forced to use her left hand for all purposes owing to injury at the age of 17 years, in the other case, there were two tubercles in the right temporosphenoidal lobe and aphasia is reported to have appeared only when the patient was already moribund, and—according to Oppenheim's assumption—as the result of toxic action on the auditory speech center in the left side of the brain

On the other hand, sensory aphasia was absent in a case of tumor of the left temporosphenoidal lobe reported by Westphal,<sup>36</sup> but here the patient was left-handed

These anomalous cases in no way disprove the overwhelming evidence which establishes, as securely as anything can be in medicine, that in right-handed persons destruction of the posterior part of the left superior temporal gyrus will produce inability to understand heard speech, and abolition of all memories for spoken words, that destruction of the left supramarginal and annectant gyri will cause failure to understand writ-

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35 Oppenheim Quoted by Bruns in *Geschwulste des Nervensystems*

36 Westphal Bruns in *Geschwulste des Nervensystems*



ten speech or even will abolish the power of recognizing familiar objects, and that failure to recollect the name of an object seen and recognized will follow the destruction of the association tracts between these two centers

Variations in bulk, position, and rapidity of growth, in tumors of the temporal lobes produce changes in the degree, and to a lesser extent in the type, of speech defect found in different cases, but there is one characteristic which may be said to be constant a depression of the power to recall words, especially the names of persons, places and objects. This word-forgetfulness may be manifest in two different ways, either as inability to recollect a name in the course of ordinary conversation, or a failure to name an object of which there is visual recognition. At first sight there may appear to be no essential difference between these two defects, but it must be pointed out that the former depends on a depression of function in the cortical area containing the memories of words, while the latter arises from an interruption of the subcortical tracts uniting the visual and auditory centers.

Patients suffering from a functional deterioration of the auditory word centers do not experience true loss of word memory, the memories are for the most part still intact, but their facilitation for the moment becomes more difficult and the patient is unable by force of will to bring them above the threshold of consciousness, below which they lie latent and beyond his conscious grasp.

Abundant proof of this statement will be forthcoming when we consider the speech defects of these patients, but to illustrate my meaning a conversation with H. G. (Case 7) may here be quoted.

"I went to see Dr. Jacob                      No! not Jacob                      What's his name?"  
 Here he looked at the card above his bed on which was printed the name of his physician. "Taylor! that's it."  
 "How did you go to his house?"  
 "I went by the underground terminus                      No! what do you call the thing?"  
 "Twopenny Tube?"  
 "No! that's not the name."  
 "London Central Railway?"  
 "Yes! that's it."  
 "Where did you get out?"  
 "Oxford Terminus                      No!                      "  
 "Oxford Circus?"  
 "Yes! that's the name."  
 "Where did you go then?"  
 "You take two stations."  
 "Stations?"  
 No! turnings                      that's it                      to Wegley Street                      No!  
 Welbeck Street."

From this it is evident there was neither word-blindness nor word-deafness, further, word-memories were not impaired, but merely sub-



distress is produced—but a minute later the identical error again is made

A bunch of keys was shown in Case 6

"I know those                      made of wood                      No' of iron"

"What are they for?"

"To lock the door with                      I can't think of the word"

Shown a pocket knife—"a shovel put in a pocket", when given the opened knife he shut it and said "knife" at once

Shown a pencil "shovel," but when it was given to him he used it correctly

Shown a watch he named it properly but on being then shown a match he said "watch chain," yet when it was given to him he made the movements of striking a light

When shown a handkerchief he said "watch                      no' handkerchief",  
but a penny being then produced he said "handkerchief                      handkerchief  
handkerchief                      No' penny!"

Verbal perseveration in spontaneous speech is the result of decreased excitability of the auditory word center and occurs physiologically in fatigue<sup>38</sup> and old age. But the preponderating factor in the causation of perseveration of inapt expressions, in spite of visual stimuli, received and comprehended, must be a loss of function in the occipitotemporal association fibers.

So far were these patients from being word-deaf that often the auditory path was the only avenue by which recollection of words could be stimulated, and it must be emphasized here that not one of the five patients—5, 6, 7, 8, 9—in whom the growth occurred in the left hemisphere producing difficulty in the recollection of words, had the slightest degree of word-deafness. Spoken commands were accurately performed, their verbal mistakes were immediately recognized as such on being uttered and heard, and their power of discrimination of the value of words was exhibited by the fact that an inaccurate prompting was invariably rejected.

Reading aloud and copying were both well and intelligently carried out, writing to dictation was less well performed. As an example of spontaneous writing in which as in other cases, word forgetfulness and perseveration are manifest, may be appended a letter written by Patient 7 to a friend who was ill.

Dear Tom  
I hope you are in good in  
health ~~But~~ ~~neither~~ can you health  
it stay it is a ~~the~~ good health you will  
get the doctor the health to find better  
Yours truly  
H. H. H.

Fig. 1—Letter written by Patient 7, showing loss of word recollection and perseveration of error.

Before leaving the subject of the type of aphasia found in these patients it may be stated that in no case was there any defect in articulation, and that the four patients in whom the growth was in the right hemisphere, failed to show any disability in speech whatsoever. In all these cases the patients were right-handed.

### *Special Senses*

**Taste and Smell** Notwithstanding the evidence of irritation of the olfactory and gustatory centers, which was obtained in so many of these patients, in no case was there absolute loss of the sense of smell or taste, in only one (Case 2) was there relative loss, and it was uniformly bilateral.

**Hearing** Cases have been described from time to time of complete unilateral deafness, resulting from destruction of the opposite auditory center, but this effect has not been experimentally obtained. Moreover, Gowers<sup>39</sup> is opposed to the possibility of such a condition being other than transient, and the same contention is maintained by Bruns,<sup>40</sup> who states that acute lesions of one or other auditory centers are accompanied by a merely temporary deafness in the opposite ear. Further, on anatomic grounds, owing to the incomplete decussation of the cochlear fibers of the auditory nerves,<sup>41</sup> each auditory center is probably connected with both labyrinths. Munk affirms the contrary, but Lewandowsky<sup>42</sup> has experimentally proved that dogs retain perfect hearing after the removal of the labyrinth and auditory center of the same side.

Beevor<sup>2</sup> quotes three cases, one of complete, and two of partial deafness in the ear away from the tumor, but he does not state the condition of the peripheral auditory apparatus.

Two of my nine patients heard imperfectly on the side contralateral to the tumor, another (Case 6), whose tumor was on the left side, was unable either by air or bone conduction to hear in the right ear, this condition was of old standing, and was attributed by the patient—a gunner—to a big-gun practice, after which he had suffered from considerable right-sided earache without deafness, it was not until a few months later that he noticed that his hearing was defective.

In these three cases the tympanic membranes were normal.

In my other cases hearing was unaffected and we must conclude that in temporal tumors, auditory compensation by the opposite center usually occurs *pari passu* with the tumor growth.

Visual acuity was affected to the extent stated in each case (see appendix) merely by the changes associated with papilledema. The

39 Gowers, Sir William. *Diseases of the Nervous System*, II, 284.

40 Geschwulste des Nervensystems.

41 Schafer and Symington. *Quain's Anatomy*, III, part 1, p. 139.

42 Lewandowsky. *Die funktionen des zentralen Nervensystems*, Berlin 1907.

improvement in vision which ensued after operation while not differing from that hitherto recorded, is worthy of special consideration, as it emphasizes the advisability of operative interference at the earliest possible date in all cases of cerebral tumor in which papilledema is present

CASE 1—Admission right, 6/21, left 6/12 Discharge right, 6/9, left 6/6

CASE 2—Admission right 6/60 left, 6/30 Discharge, right 6/12, left 6/12 6/9 with binocular vision

CASE 3—Admission right 6/21 left, 6/12 Discharge, right 6/9 left 6/6

In Cases 5, 6 and 7 visual acuity materially improved after operation and no detailed examination was made before discharge

#### *Cranial Nerves*

The first and second cranial nerves have already been considered

The proximity of the third nerves to the temporal lobes would seem to render them especially liable to damage by pressure from tumors in these areas, and Knapp<sup>13</sup> lays considerable stress on homolateral or, less frequently, crossed partial third nerve paralysis, as a diagnostic sign of tumors of the temporo-sphenoidal lobes. In none of these cases was this result observed, nor was it present in the other cases of temporal tumor which have come under my observation

When a temporal lobe is the seat of abscess it is, however, not very uncommon to find ipsilateral ptosis, mydriasis and external strabismus—a statement which agrees with Bruns' experience, and has been emphasized by Riesen Russell in the Lectisoman lecture for the present year

Three patients had a history of transient diplopia, probably due to temporary increase of pressure on the third or sixth nerves, in two, the ipsilateral pupil was myotic though active to light and on convergence, while in the same patients there was nystagmoid jerking of the eyeballs on conjugate deviation to one or other side—probably a pressure-effect on the cerebellum

The fifth nerve was in all cases unaffected

#### *Seventh Nerve*

Peripheral affection of this nerve was in all cases absent, but in no less than five out of the nine patients there was marked supranuclear weakness of the face contralateral to the tumor out of all proportion to the degree of paresis of the limbs of the same side

This striking fact is, however, only corroborative of Horsley's statement<sup>14</sup> in 1895, that in those temporal tumors the pressure of which is directed upward there is definite sequence in the progress of the paralysis, it being more marked first in the face, then in the upper, and last of all

<sup>13</sup> Knapp Quoted by Bruns in *Geschwulste des Nervensystems*

<sup>14</sup> Horsley, *St. Victor Clin. Jour.*, Lond., v, 249

in the lower extremity In four of these five cases, however, in which the face was markedly affected, another point was noticed, that, contrary to what is usually seen in facial paresis of supranuclear type, the emotional expression was either lost or greatly diminished on the affected side

There can be no doubt that this condition was the result of pressure acting on the optic thalamus, which Nothnagel<sup>45</sup> and Bechterew<sup>45</sup> showed many years ago to be an important reflex center for emotional expression

The phenomenon was best shown in reflex action, as when the patients were made to laugh by being tickled, when this was done to the eighth patient, in whom the condition was most noticeable, the left side of the face wrinkled in laughter, while the right side remained motionless and smooth for some five seconds, after which the right angle of the mouth was elevated, but to a much less degree than that of the opposite side

Acuity of hearing has already been referred to

The remaining cranial nerves were unaffected

#### *Motor Symptoms Apart From Those Due to Affections of the Cranial Nerves, Deep and Superficial Reflexes*

Patient 1 said she felt that her left arm and leg were weaker than their fellows, but examination failed to show any difference in strength between the two sides Her gait was normal The deep reflexes were everywhere brisk and respectively equal on the right and left side Both the plantar responses were of the flexor type, but the left abdominal reflexes were markedly depressed, and on repeated stimulation tired much more quickly than the right

Rosenbach was the first to point out in cases of hemiplegia the absence of the abdominal and epigastric reflexes on the side of the affected limbs and now they must be regarded as the most sensitive indication of commencing pressure on the pyramidal tracts

Grainger Stewart<sup>46</sup> has pointed out their significance in cases of frontal tumor, in which there is backward pressure on the precentral cortex, and their importance in this series is apparent, as in five cases their inequality was a material aid to diagnosis

The second patient was without motor symptoms, when she came first under observation, but in the course of the following six weeks her left leg gradually became weak, though it was not possible to detect any loss of strength in the left upper extremity

This evidence of slowly cumulative pressure on the peripherally placed leg fibers of the internal capsule corroborated that given by the condition of the reflexes of the left side, the superficial being depressed

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45 Soury, Jules Le systeme nerveux central, 1343 1344

46 Stewart, T G Lancet, London, 1906, p 1209

and the deep  $\kappa$  exaggerated, though the left plantar response remained of the flexor type except for a short time after the patient's only major epileptic attack.

In the third case the depression of the left abdominal and epigastric reflexes was the sole indication of pressure on the pyramidal fibers; there was no loss of power in any limb and the gait was normal. Neither patellar nor Achilles tendon reflexes were ever obtained, and this fact together with the presence of double pes cavus, gave rise to the suspicion that Friedreich's disease might be a complicating factor; there was no further clinical evidence to support this hypothesis, and no degeneration was later found in the posterior or lateral columns of the spinal cord.

Degeneration in the posterior column of the spinal cord has been shown to occur with considerable frequency in cases of intracranial tumor, as a result of traction on the posterior roots by meningeal distention produced by increased intracranial pressure.<sup>47</sup>

The presence or absence of the deep reflexes has been usually directly dependent on the degree of this posterior spinal change, but absence of the knee-jerks in cases of intracranial tumor has been observed, when no demonstrable change had occurred in the cord,<sup>48</sup> particularly in those cases in which the growth was situated in the temporo-sphenoidal lobes.

Patient 1 had no loss of power in the limbs, nor were his movements ataxic while he remained in bed; however his attempt to stand upright was very badly performed, he swayed directly backward, and in trying to maintain his balance took several quick steps backward on his heels, and would certainly have fallen had he not been supported. He said he had no dizziness but that he "just could not stand up straight."

Titubation of this kind has been described before as occurring in cases of temporo-sphenoidal tumor, and Sir Victor Horsley<sup>49</sup> is inclined to regard it as due to interference with Trunk's bundle, which unites the pons and the posterior part of the temporo-sphenoidal lobe, where Mill<sup>50</sup> assumes the existence of a center for orientation.

An identical phenomenon was observed in three more of my series (Nos. 5, 6 and 9), where it appeared, however, somewhat late in the course of the disease, when intracranial tension had become extreme, and cerebellar compression against the edge of the foramen magnum could no longer be excluded.

The condition of the reflexes in my fourth case was interesting: the left knee-jerk and both ankle jerks were absent, the right knee-jerk was much depressed, the abdominal and epigastric reflexes were not obtained on either side, while the deep reflexes in the upper extremities were equally brisk. The suspicion of *tabes dorsalis* being coexistent with cerc-

47 Batten and Collier. *Brain*, 1899, xii, 471 *et seq*.

48 Mackenzie, Sir Stephen. *Brain*, 1884, vi, 22.

49 Horsley, Sir Victor. *Tr. Otol. Soc., London*, 1905, vi, 77.

bial tumor was negatived during life by a cytological examination of the cerebrospinal fluid, and no degeneration was later found in any part of the spinal cord

On admission to the hospital, my fifth case was entirely without motor symptoms, but the advent of right-sided weakness was heralded by a marked depression of the abdominal reflexes on the same side, it is to be noticed that by these alone the diagnosis as to the side of the tumor in the intracranial cavity could have been made two months before any weakness was found in the arm or leg of the same side

Case 5 had no definite weakness in any of the limbs, the abdominal reflexes could not be obtained, probably because of the obesity of the patient, the plantar responses were both of the flexor type, but there was undoubted exaggeration of the deep reflexes of the right arm and leg

In Case 7 the right arm was definitely weaker than its fellow, and the abdominal reflexes on the same side could only rarely be obtained, though those on the right were invariably brisk. There was change neither in quality nor degree in the plantar and deep reflexes

In neither of the two remaining cases was there any affection of the limbs, nor were the reflexes altered in character

The abdominal reflexes were not obtained in Case 8 until after operation and the relief of pressure they were then found to be brisk and equal on the two sides

The sole patient of this series who at any time had objective sensory change was V F (No 1), who after the removal of the growth had slightly diminished acuity in appreciation of touch and pain on the left side of the body

Appreciation of cutaneous pain and touch on the left hand was very slightly less than on the rest of the left side, but on the left hand touch sensation was very badly localized, pressure-pain was almost absent, and there was complete loss of the sense of position and of passive movement in the left wrist-joint and the finger-joints of the left hand

As a result of this condition she was completely astereognostic in this hand, from which she frequently let objects fall, if she failed to keep her eyes fixed on what she carried. In March, 1910, she was in excellent general health and the sensory condition of her left hand was her sole complaint

T G Stewart<sup>46</sup> has stated that loss of sphincter control is a frequent occurrence in cases of temporosphenoidal tumor, but such a condition was never present in any of these patients as long as consciousness was retained

I do not purpose to detail the various considerations which led to correct diagnoses in all these cases, on all-important points emphasis



has already been laid but to summarize them here may be convenient. Headache of varying severity and epileptiform convulsions are usually features of the beginning of the disease. Fits may be very slight at first, consisting merely of loss of consciousness, a momentary tonic and clonic, but a careful cross-examination will often elicit evidence of greater affection of one or other hemisphere. The presence of major attacks of this description may overshadow in the mind of the patient the occurrence of less pronounced seizures in which consciousness is retained under altered conditions. A rightly directed examination will speedily discover such if present but we cannot expect all patients spontaneously to describe apparently negligible phenomena if we ourselves fail to be alive to their vital importance. A history of crude subjective sensations of taste and smell occurring either alone or as the precursor of epileptiform convulsions is of course of the first importance in the localization of disease in one or the other temporosphenoidal lobe nor does it appear that we need expect any corresponding loss in acuity in the gustatory or olfactory senses.

Papilledema is usually present, usually intense, and usually more severe on the side of the tumor.

The presence of crossed facial palsy particularly if it be of affective character is especially valuable if the other signs of hemiplegia be doubtful. Particular stress must be laid on the condition of the abdominal and epigastric reflexes. These, with papilledema of greater ipsilateral severity and subjective auditory sensations of somewhat equivocal nature were the sole positive signs in my third case. One of negative character was the complete absence of any defect in speech.

Word-forgetfulness has invariably been present in all my left-sided cases, though often to a very slight degree, even where it is not evident, it can be demonstrated if the examination be properly carried out and tests should be mainly directed to the discovery of the ability of the patient to name known objects.

Word-forgetfulness was the only sign of localizing value in Case 9, and on it alone a correctly planned operation was performed.

The difficulty in the diagnosis of temporosphenoidal tumors, and in the localization of them in the right or left side of the brain arises not from the absence of indicating signs, but rather because signs, though present, are often not striking, are not looked for, and consequently are not seen.

#### *Symptom-Complex of Tumor in the Right Temporosphenoidal Lobe, in a Right-Handed Person*

Epileptiform convulsions, of varying severity and frequency, dreamy states or analogous pathological psychical conditions, crude subjective sensations of smell or taste with or without involuntary reflex move-

ments of mastication. Subsequent to major attacks in most cases, transient weakness of the left lower facial muscles, usually most evident on emotional expression, less often the left arm and leg temporarily paresed, left abdominal reflexes diminished or absent, deep, increased, the left plantar reflex may be of extensor, and the right of flexor type.<sup>50</sup>

Bilateral papilledema, usually of greater intensity on the right side. Reflex change and motor symptoms on the left side, at first merely post-epileptic, but later become persistent phenomena.

No word-forgiveness after major attacks nor at other times. No speech defect whatsoever.

*Symptom-Complex of Tumor in the Left Temporo-sphenoidal Lobe, in a Right-Handed Person*

Difficulty in naming objects seen and recognized, later, word-forgiveness in conversation, later, inapposite words and phrases, with instant recognition of mistake when made, but inability to prevent perseveration of verbal errors.

Reading aloud and writing to dictation are well performed. Spontaneous writing, poor.

Epileptiform convulsions of varying severity and frequency, dreamy states or analogous pathological psychical conditions, crude subjective sensations of smell or taste, with or without involuntary reflex movements or mastication. Subsequent to major attacks in most cases, transient weakness of the right lower facial muscles, usually most evident on emotional expression—less often, the right arm and leg temporarily paresed, right abdominal reflexes diminished or absent—deep, increased, the right plantar reflex may be of extensor and the left of flexor type.

Bilateral papilledema usually of greater intensity on the left side. Reflex change and motor symptoms on the right side at first are merely postepileptic, but later become persistent phenomena.

#### APPENDIX ABSTRACT OF CASES

CASE 1—*History*—V. F., female, aged 39, was admitted on June 15, 1908. From the age of 14 she had had, at intervals of three to six months, epileptic fits of ordinary character, but without aura. In May, 1907, she, while dressing, suddenly heard a bell ringing, then saw a "strange bad woman" clad in rags, and smelt a most evil odor, which originated, she thought, in the stranger's clothes, patient then complained of a feeling of dread, associated with nausea, pain in the precordia and epigastrium, and tingling throughout the inner aspect of the left upper limb. For some seconds she seemed dazed and frightened, then screamed, suddenly became unconscious, and passed through all the stages of a severe epileptic attack which in no way differed from her previous fits. A short

<sup>50</sup> The presence of hemianopia or hemihemiparesis would of course indicate the side of the lesion, vide case reported by author at the New York Neurological Society, March, 1911.

period of drowsiness immediately followed and then while yet dazed, the patient was very voluble but subsequently she had no recollection of having spoken. Between May 1907 and June 1908 she had two or three less severe epileptic fits each of which was preceded by nausea vomiting and intense headache mainly over the right occiput. In each of these attacks the auditory visual olfactory and parasthetic aura just described were accurately reproduced. At no time was there any word forgetfulness or speech defect.

*Examination*.—Vision. Right 6/24 left 6/12 fields concentrically diminished especially right intense papilloedema with hemorrhages on both sides right  $- 8D$  left  $+ 6D$   $+ 3D$  hypermetropia in each eye. Left pupil slightly larger than right fine nystagmoid jerking on lateral movement especially to left no diplopia ptosis nor strabismus oculi movements good weakness of left lower facial muscles especially evident in emotional expression all other cranial nerves normal. Motor. Subjective weakness of left upper extremity only no sensory changes abdominal and epigastric reflexes were depressed but more markedly so on left side the deep reflexes were not appreciably affected.

*Operation*.—A well defined deeply situated subcortical tumour about the size of a fingertip or orange was removed from the anterior part of the right temporal sphenoidal lobe.

*Postoperative History*.—Four hours after operation the patient suddenly said she was going to have a fit she experienced the same aura as before after which her left forearm flexed little finger and thumb extended other fingers flexed and a series of slow alternating flexion and extension movements of the wrist began and continued for ten minutes consciousness was retained throughout. On August 11 patient was discharged in good general health. Mental state was normal there was no speech defect. The swelling of the disks was rapidly subsiding. There was slight weakness of the left lower face and left arm complete astereognosis in the left hand with some diminution of tactile sensibility of the left side of the body. In March 1910 the only pathological sign to be found was a loss of sense of position and of passive movement in the left wrist and finger joints.

*Tumour*.—Weight 110 gm. glomtuous but sharply demarcated from surrounding brain tissue, tumour cells formed palisade arrangement around vessels many of which contained organized clot marked fibrous degeneration and thickening of vessel walls.

*CASE 2—History*.—1. M. female aged 32 admitted July 24 1907 from 1905 had been subject to a sudden inexplicable feeling of profound fear which lasted for one to three minutes and left her weak and trembling. From January, 1907, she could distinguish two types of seizure.

1. Major. Usually once every day the patient felt overpowered by drowsiness, 'as if on the verge of sleep' and 'everything seemed remote, unnatural and unreal', she could always recollect her experiences of these attacks, which were associated usually with a consciously subjective and groundless sensation of terror, and unnatural buzzing whirling sounds in her head. Her children noticed that she always "twisted her mouth about and made sucking, champing movements" just previous to an attack.

2. Minor. These were slight attacks of inconstant character, but always consisting of unaccountable sensations, essentially unhappy, despairing, or uncomfortable. From Easter, 1907, the patient had frequent frontal headache and nausea, but rarely vomited, from the same period her vision rapidly deteriorated, till she was unable to read or sew. She never had diplopia, nor any speech defect.

*Examination*.—Intelligence and memory good. Smell and taste much impaired on both sides. Vision. Right 6/60, left 6/30, visual fields irregularly contracted, no hemianopia, swelling of right optic disc  $+3D$ , of left  $+5.5D$ , early atrophic changes in both. Paresis of supranuclear type of left facial muscles. No defect in other cranial nerves. Motor system normal. No objec-

tive sensory changes, frequently numbness and tingling in left face, preceded attacks. No sphincter trouble. Left abdominal reflexes diminished and readily fatigued, tendency to left ankle clonus, left plantar response less definitely flexor than right.

*Course of Disease*—August, 1907. Subjective sensations of smell first appeared; each subjective odor persisted for about ten minutes, recurred several times daily, was neither pleasant nor unpleasant, and seemed always unreal and to arise external to, and to the right of, the patient.

September 7. Vision right 3/18, left 3/12, greater paresis of left lower face. Deep reflexes on left brisker than on right. Left abdominal reflexes greatly diminished. No other changes in former state.

October 16. Unconsciousness and general convulsions with a doubtful origin in the left face. Five minutes after recovery left facial weakness very marked, left abdominal reflexes absent, right present. Left plantar response, extensor, right, flexor.

October 29. Right temporal lobe exposed, and was found to be the seat of a hard, diffuse immovable growth.

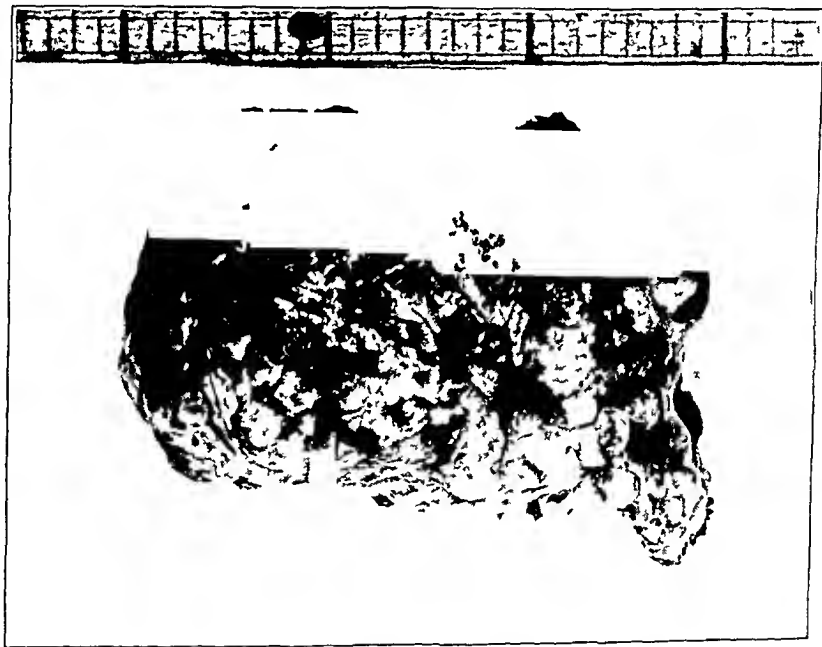


Fig. 2.—Tumor removed from Patient 3. Endothelioma weighing 92 gm.

February, 1908. General health excellent. No headache nor vomiting. Attacks decreased in frequency and severity. Marked subsidence of swelling of optic disks. No subjective sensations of smell, no speech defect.

*CASE 3—History*—T. B., male, aged 21, admitted Aug. 13, 1909. He, his maternal grandfather, mother, and brother, had all double pes cavus. From August, 1908, he had had three monthly attacks of severe frontal headache, nausea and vomiting, which lasted nearly twenty-four hours every three months. About June, 1909, slight dimness of vision developed, and four weeks later he was almost blind in the left eye. In July, 1909, a persistent "singing or buzzing" of increasing severity arose in the right ear, and just before admission the headache and vomiting recurred.

*Examination*—Smell, Taste and Hearing Normal. Vision Right, 6/12, left, only light perceived. Fundi Intense papilledema, 6D of swelling in each disk, with macular striation. No other cranial nerves affected. No motor nor sensory defect. No tremor of tongue, knee and ankle jerks absent with depic-

sion of deep reflexes in upper extremities. Plantar responses of flexor type. Abdominal reflexes on left markedly elicited and easily fatigued on right brisk. Intelligence, attention and memory good. No speech defect or word forgetfulness.

*Operation*—On August 20 a large tumor which involved the petrous portion of the temporal bone and which lay wholly below the Sylvian fissure, was removed from the right temporosphenoidal lobe.

Consciousness returned immediately after the operation and was retained till ten minutes before death which occurred six hours later. During his conscious life after operation there was no evidence of mental depression, difficulty in speaking, word forgetfulness, nor motor nor sensory paralysis.

*Autopsy*—Encapsulated tumor weighing 92 gm. composed of endotheliomatous cells without typical whorl arrangement. Anterior surface of petrous bone needed for a short distance. Tympanic cavity not invaded. Brain convolutions much flattened. Into formation of tumor bed all three temporal convolutions entered. Upper limit, 1 cm. from fissure of Sylvius, lower, hippocampal convolution. Brain compressed but not infiltrated.

*Case 4—History*—B. C. male aged 49 admitted Sept. 9, 1908. From June 1908 he was subject to frequent sudden "attacks of giddiness" in which he felt dazed but did not lose consciousness. With each attack he experienced a horrid smell and a nasty taste like ink and occasionally had in addition involuntary twitchings in the right arm. After July, 1908, he had three attacks of loss of consciousness and cyanosis without involuntary movements or relaxation of sphincter control. Occasional vomiting and frequent nausea during July and August. Frontal headache became severe in September, transient diplopia during the week before admission.

*Examination*—Attention poor, patient talkative and excited, no speech defect, named seen objects perfectly. Cranial nerves normal except for intense swelling of both optic disks. Large recent retinal hemorrhage in the left eye.

Marked tremor in hands. Gait. On standing he carried himself solely on his heels and would have fallen straight backward had he not been supported.

Sensory system apparently normal.

Reflexes of the upper extremity brisk and equal on the two sides.

Right knee jerk present, left knee jerks not obtained. Ankle jerks not obtained.

Plantar reflexes indefinite in character. No sphincter trouble. Cerebrospinal fluid normal.

*Course of Disease*—September 10. Patient suddenly looked dazed and frightened, lay back in bed, marked flexion and extension movements at right elbow joint. No march or spread of movement. Patient was asked if he could not keep his arm at rest and answered distinctly "No, I can't." Attack lasted about three minutes.

September 11. Patient suddenly became unconscious and greatly cyanosed. Breathing stertorous. Plantar reflexes both of extensor type.

He gradually sank and died four hours later.

*Autopsy*—Right temporosphenoidal lobe was softer and larger than left.

Section 1 along Sylvian fissure. Both lateral ventricles much distended and filled with blood stained fluid. Cortex of anterior part of right superior temporal convolution was abnormally hard with loss of differentiation between gray and white matter. Choroid plexus in lateral ventricles contained a few small cysts.

Section 2, 2 cm. lower. Tumor mass exposed, circuli in outline, about the size of a tangerine orange. It lay about 2 cm. from the tip of the right temporosphenoidal lobe and reached to within about same distance from external aspect of lobe. It was external and anterior to the internal capsule and was the seat of a large recent hemorrhage. Much softening round tumor. Posteriorly, soft-

ening was extreme and the wall of the right lateral ventricle had given way, the posterior and descending horns were occupied by a gelatinous and blood stained mass of debris (Fig 3)

Section 3 through the tip of right temporo-sphenoidal lobe. The most extensive site of the tumor, which occupied most of the antero internal part of temporo-sphenoidal lobe. Posteriorly the growth had involved the wall of descending horn of lateral ventricle. The uncus and pes hippocampi were intact.

Pons upper quarter of the Sylvian aqueduct dilated, old and recent hemorrhages.

Some clot in Sylvian aqueduct. No hemorrhages below the superficial origin of the fifth nerve.



Fig 3—Brain from Patient 4. Section showing right temporo-sphenoidal tumor.

The spinal cord was normal.

On microscopic examination the growth was seen to be glomatous.

CASE 5—*History*—F J B, male, aged 30, admitted July 7, 1908, on May 10, 1905, he suddenly felt dizzy and then for fifteen minutes was unconscious without convulsions or relaxation of sphincters. Subsequently he was subject to attacks which consisted of a "dazed and queer feeling" without loss of consciousness. From June, 1908, severe headache occurred, rarely accompanied by nausea and vomiting, usually in the early morning. From January to June he had difficulty in making himself understood, 'he often used the wrong words', and his memory gradually failed. Transient diplopia first appeared in June, 1908 and often recurred.

*Examination.* Attention markedly variable; patient frequently unable to reply because he cannot explain answers; odors richly differentiated but rarely named; at first prompting is required whilst correct is at once accepted. Vision right 6/10, left 10/10, no homonymous; intense papilledema; right swelling 5D, left 10D; numerous retinal hemorrhages especially in left; coarse nystagmoid jerks of eyes on conjugate deviation to right; definite weakness of right lower facial muscles; no accident in emotional expression; no loss of power in limbs but marked tremor in right hand; reflexes normal, except right abdominal reflexes depressed; sensory system normal. Sudden attacks in which the patient seemed excited and only remotely conscious were many times observed, in only one were there motor symptoms: a series of rapid movements of alternate flexion and extension at the right elbow joint, neither associated with paresthesia nor followed by weakness.

A large cystic glioma mainly subcortical but reaching the surface in the middle third of the middle temporal convolution on the left side was removed. Word forgetfulness was subsequently greatly increased and was still very evident on patient's discharge two months later.

*Pathological Report.*—Tumor weight 65 gm., center consisted of organized blood clot. Blood supply contained in vascular spaces and embryonic vessels; very cellular, made mainly periphrical stromal scanty glioma.

*CASE 6.—History.*—A S. I. male, aged 35, was admitted in May, 1908. In the winter of 1906-1907 he became sleepless and irritable and was conscious of a gradual loss of memory. He was moody and suspicious and for a short time was troubled by a sense of being persecuted; unsteadiness in walking and weakness with clumsiness of the right upper limb gradually developed so that although he continued to work his usefulness was much diminished. In the summer of 1907 he often "looked dazed and lost," felt faint, and had weakness and tremor of the right arm and of both legs especially the left but never paresthesias. In November he was noticed often to have difficulty in finding words but his attention was unimpaired. During November and December he frequently vomited but afterward he never suffered even from nausea.

*Examination.*—Attention very variable, patient recognized and appreciated the use of objects usually without being able to name them correctly; tendency to repetition of the same verbal error; no word deafness, on command, patient could select one of the several objects displayed and could correctly perform simple tasks. Patient could not name odors but could distinguish one volatile substance from another and alleged he recognized each. Taste normal. Vision right 6/8, left 6/18, bilateral papilledema, right + 5D, left + 6D, the swelling more recent in right, no homonymous. Right deafness—neither bone nor air conduction, tympanic membranes normal. Other cranial nerves unaffected. No sensory loss. No sphincter disturbance. No weakness or ataxia in the limbs, but patient stood solely on his heels and when unsupported staggered straight backward. On extension of right upper limb coarse tremor appeared in hand, right knee and ankle jerks greater than left, both plantars of flexor type.

*Operation.*—A hard, light yellow, deeply subcortical tumor about the size and shape of a golf ball was found in the left temporosphenoidal region, its removal was performed in two stages. Weight of growth 65 gm. A columnar celled carcinoma.

*CASE 7.—History.*—H. G., male, aged 40, admitted July 31, 1908, on May 8, suddenly had a sensation as of "a vapor in the mouth, like the smell of smoke of coarse tobacco from a foul pipe," and lost consciousness for fifteen minutes. On recovering, he apparently understood all that was said to him, but until the following day he could not speak intelligibly. Subsequently for several days he had headache, weakness and numbness in the left arm and leg, and for three weeks felt too feeble to work. In June and July similar attacks preceded by the same aura and followed by a similar grave difficulty in expressing his thoughts, frequently recurred. In June his gait became unsteady, and "pins and

needles" sensation arose in both legs. From July 12 he had severe constant head ache and marked failure of memory and attention. He never had sphincter trouble.

*Examination*—Attention poor, memory for events good, marked word-forgetfulness, elliptical speech, tendency to recurrence of some verbal errors, instant and spontaneous recognition of mistakes, no word deafness, articulation good. On admission no swelling of optic disks, some distention of fundal veins, ten days later slight swelling of left disk. Supranuclear type of weakness of right lower facial muscles, weakness of right upper extremity without spasticity. Lower extremities, no loss of power, on standing, patient staggered backward on heels, the toes being strongly dorsiflexed, no sensory changes, deep reflexes all brisk and equal, right abdominal, diminished and easily fatigued, left, active

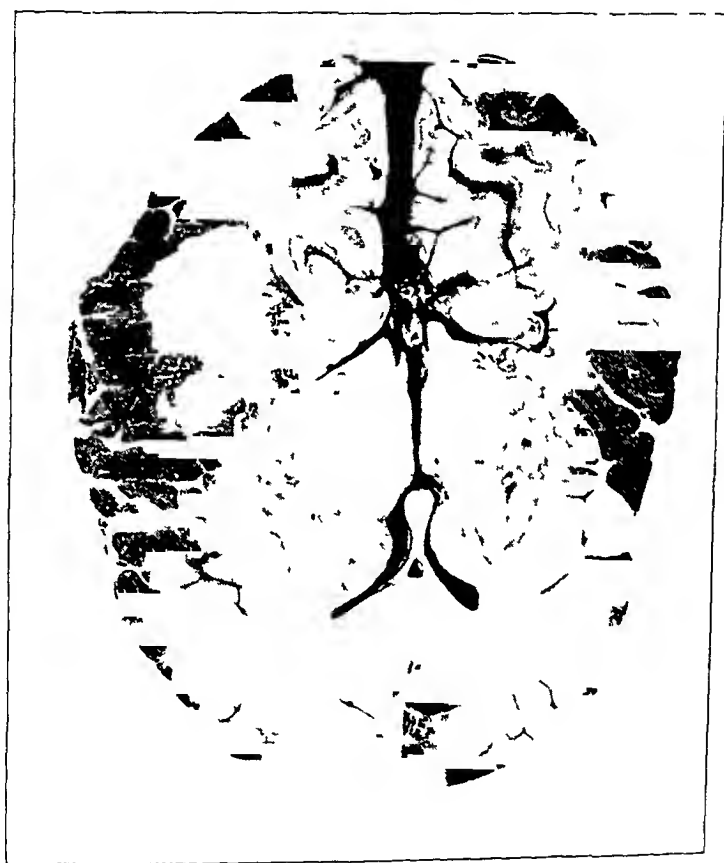


Fig. 4—Brain of Patient 9. Left temporo-sphenoidal tumor. Horizontal section through basal ganglia.

and persistent. Plantars both flexor. August 28, occasional right, extensor, left always flexor.

*Operation*—This displayed a large diffuse and nonremovable growth, apparently of malignant nature, deeply situated in the posterior and upper parts of the left temporo-sphenoidal lobe.

Operation well sustained.

**CASE 8—History**—R. F., female, aged 35, admitted Nov. 19, 1909, from 1907 had frequent general epileptic fits, often associated with severe headache and vomiting. Almost all attacks were preceded by a subjective sensation of smell and taste "like rotten fish," and less often by "a sound like some one singing," and were usually followed by marked difficulty in the recollection of words and





Fig 5—Brain of Patient 9 Section below basal ganglia

cortex instantly bulged through the dural incision and burst a few seconds later, emitting a jet of yellowish fluid. Exploration of the cavity thus opened proved it to be merely the dilated lateral ventricle, from which was removed a small hard tumor, growing from the choroid plexus and adherent to the tapetal margin.

*Postoperative History*—For two days patient had no postoperative symptoms and no increased difficulty in speech.

Dec 2, 1909 Patient in good general health, but completely unable to express her thoughts, words were slowly and distinetly uttered, but were quite inapt and without meaning, her errors caused patient much distress. Commands were perfectly understood and performed.

Dec 13, 1909 Patient in excellent health Vision, right 6/9, left 6/6, marked subsidence of optic disk swelling Right facial weakness much diminished No paresis of the limbs Word forgetfulness only rarely present No apraxia No attacks of crude sensations

Jan 14, 1910 Patient left hospital without symptoms

CASE 9—*History*—J M C, female, aged 33, was admitted on May 14, 1909 May, 1904, she had a sudden attack of unconsciousness with general convulsions, in which her tongue was bitten She was subsequently quite well till November, 1907, when she had another fit of sudden unconsciousness but without involuntary movements April, 1908, she began to complain of nausea but vomited only once In May, 1908, headache developed and gradually became more constant and severe, from the same time she often found she could not accurately name familiar objects, she would, for example, in these transient periods of word forgetfulness call a clock "a watch," etc, but she was always at once aware of her mistake, from this date also she was subject to momentary losses of consciousness From December, 1908, she was unfit to work, she did any task very slowly, was easily tired, spoke seldom and hesitatingly as if at a loss for words but her articulation was unaffected From March, 1909, her vision which had then been slightly defective for nine months became rapidly worse, and transient diplopia, and brief spells of blindness often occurred For several months before admission she frequently "had a bad taste in the mouth" which rarely was followed by loss of consciousness

*Examination*—Attention and memory poor, mental processes slow but clear, marked word forgetfulness with perfect articulation, but halting elliptical figurative speech, cranial nerves normal except for intense swelling of both optic disks, motor and sensory systems normal, gait and reflexes unchanged

On the evening of May 16, coma suddenly supervened, a decompressive operation was at once performed over the left temporal region, but patient died two hours later

*Necropsy*—Left temporosphenoidal lobe considerably enlarged, slight pressure on left third nerve and left optic tract Soft infiltrating tumor containing recent hemorrhages, extending throughout the center part of left temporosphenoidal lobe for 6 cm in anteroposterior direction, forward to 1 inch from tip of the lobe, inward to posterior wall of descending horn of lateral ventricle, downward to margin of cortical gray matter

Section through middle of basal ganglia and internal capsule Tumor, limited on anteromesial aspect by posterior part of internal capsule, lay completely behind posterior limb of Marie's "quadrilateral"

Mesial surface merged with area of optic radiations Microscopically Sarcoma

52 West Fifty Third Street

# FURTHER EXPERIENCE IN THE PREVENTIVE TREATMENT OF RABIES WITH UNCHANGED VIRUS FLUX

FREDERIC PROESCHER, M.D.  
MURKIN

In a previous article<sup>1</sup> I reported the result of treatment with unchanged *virus flux* in forty cases. Review of the literature on this subject shows that the ultimate result of the preventive treatment is best when the least changed *virus flux* is used.

Regardless of the good results from the exclusive use of unchanged *virus flux* obtained by Ferran and myself, no other Pasteur institute has exclusively adopted this method. The aversion to producing experimental rabies by using unchanged *virus flux* only is not yet overcome.

In my first paper I stated that Ferran was of the opinion that one injection would give complete immunity.

In my first series of forty cases the patients were treated with doses fifty times larger than given by Ferran. The first ten patients were given two injections daily, eleven one injection daily for ten days, and the remaining nineteen were given one injection daily for six days. The results by this method being very satisfactory I made a further reduction. I decreased the time to one injection daily for five days and also gave smaller doses.

I hope the following report of ninety-two cases in which the patients were treated exclusively with unchanged *virus flux* will lead to the conviction of the innocuousness of this method.

For the treatment I use exclusively the brain of rabbits infected with *virus flux*. The brain is removed and divided into hemispheres and each preserved on 50 per cent glycerin slant agar in tubes 15 by 3 cm (Figure 1). The tubes are then covered with a rubber cap to prevent evaporation and are kept in the refrigerator. This preserving method is preferable to glycerin water, being ready for use at all times and any bacterial contamination will be detected by growth on the surface of the agar.

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1 Proeschel, Frederic. A Danger free Method of Using Freshly Prepared Virus (*Virus Flux*) from the Brain of the Hydrophobic Rabbit, New York Med Jour., 1909, 26, 688.

2 The rabbits which are used for obtaining the *virus flux* are killed during the paralytic stage by bleeding from the inguinal artery about twenty four hours before the time death is expected. This method is preferable to spontaneous death because a certain amount of bacteria will enter the blood stream during the agony and the brain will not always be sterile.

As a routine measure we use a fresh rabbit brain each week, although the *virus fixe* preserved in these tubes retains its virulence from four to six weeks. For obtaining a uniform amount of brain substance we use a urethral forceps with a concave alligator jaw which, when closed, forms a small cavity which will contain an average amount of 0.10 gm. to 0.12 gm. of brain tissue (Figure 2). The sterilized instrument is opened, forced into the brain substance (Figure 3), closed and removed and the contents deposited in a sterile glass. This amount is then thoroughly emulsified with a sterile glass rod, a few drops of salt solution added until a homogeneous suspension is obtained, and is further diluted with 30 c.c. of salt solution.



Fig. 1.—Brain substance preserved on 50 per cent glycerin slant agar.

Three c.c. of this emulsion, which is equal to about 0.01 gm. *virus fixe*, is injected subcutaneously. The abdominal region is preferred.

In Table 1 my cases are grouped after the example of Pasteur, with the addition of one group in which the diagnosis is made by histological examination.

Group A contains such cases as were proved positive rabies by animal inoculation.

Group B contains cases which were diagnosed by competent veterinary surgeons.

Group C contains cases of suspected rabies, the animals, however, not having been examined.

Group D are cases diagnosed by histological examinations.

Time	Cases
1 to 3 days	56
4 to 7 days	19
8 to 14 days	13
15 to 31 days	3
37 days	1

In some of these cases the wound had been cauterized previous to admission but in no case was the cauterization sufficient to destroy the virus.

The ninety-two cases in which this treatment was used show that the preventive treatment with unchanged *virus fixe* gives constant results regardless of the decreased doses and the time of treatment.

When we consider that in other Pasteur institutes, which use the old or a more or less modified scheme of treatment by Pasteur, that the average mortality is between 0.12 and 1.28 per cent and further that it is shown by the statistics collected by Diatrioptoff that the mortality is increased with the length of time between the bite and the beginning of the treatment the entire use of unchanged *virus fixe* is without doubt superior to the other methods.

TABLE 3.—DEATHS UNDER TREATMENT WITH VIRUS FIXE

Beginning of treatment after the bite	Cases, No	Deaths, No	Per Cent
1 week	1602	26	0.56
2 weeks	961	16	1.66
3 weeks	313	10	3.19

In none of my cases has an ill effect occurred which could be traced to the use of unchanged *virus fixe*.

If it is possible to immunize animals with one injection of unchanged *virus fixe*, why not human beings? According to my practical experience with human beings, I gave large doses of unchanged *virus fixe* without danger. Therefore I conclude that one large dose of fresh *virus fixe* should give complete immunity.

By the present treatment, I give 0.05 gm. in five days. My first forty cases I gave 0.4 gm. daily or 2.4 gm. in six days. One dose of 0.1 to 0.2 gm. should give a complete protection even in the more extensive bites.



Fig. 2—Urethral forceps with concave alligator jaw

Ferran gives 0.3 gm. of fresh *virus fixe* in five days, which is probably too high since he uses only the superadjacent fluid and not the sediment. The average amount would be about 0.15 gm.

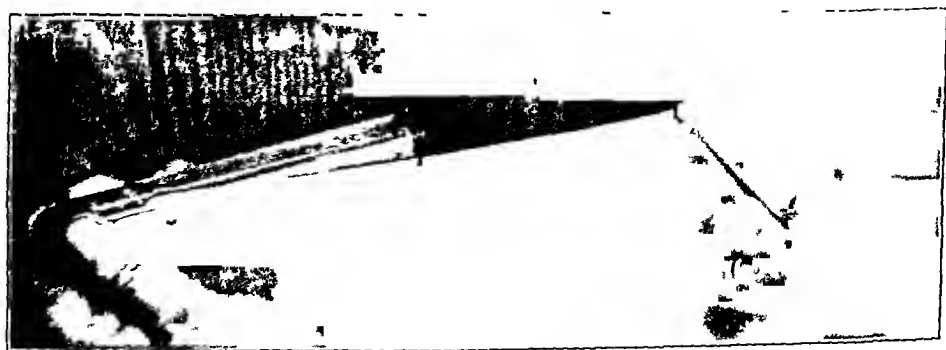


Fig. 3—Cutting brain substance with urethral forceps

I agree with Marx that one injection will immunize all human beings capable of being immunized, and that more or less duration of the incubation time need not be considered, because an incubation time of twelve days has not been definitely determined in human beings. Immunity will be produced within the limits of this time.

The danger of an intoxication from the rabies toxin, the last objection of Marx, is without foundation because the entire amount of 0.1 to 0.15 gm. is about one-fourth smaller than the first dose given to the first forty patients and without any symptoms.

Theoretically and practically there is no objection to giving one large dose of unchanged *virus fixe* both as to safety and immunity. For rapid and intensive absorption it is advisable to inject the dose in three or four different locations.

To say that mortality is reduced to the minimum by the exclusive use of unchanged *virus fixe* will have to be confirmed by use in a larger number of cases.

The paralytic symptoms observed during or after treatment with the other methods seem to be due to an abortive form of street virus infection probably due to incomplete immunity and not to the treatment with *virus fixe*.

It is necessary to keep in mind that not all the different strains of *virus fixe* in unchanged condition which are used in other institutes are entirely free from danger to human beings. Every other *virus fixe* which will be used in unchanged condition must be carefully tested before using on human beings. It is probable, however, that all the *virus fixe* is more or less avirulent to human beings as has been shown by many careful investigators.

The question arises: Can we further decrease the time of treatment without risk? I believe this question can be answered satisfactorily.

Marx showed experimentally that rabbits after one injection intraperitoneally with unchanged *virus fixe* can be completely immunized. The rabbits after the twelfth day are completely immune to intracranial infection. I can confirm Marx' experiments.

By the old Pastern method and its modifications in which unchanged *virus fixe* is not given at all, there is only a very small amount of avirulent *virus fixe* in the dried spinal cord which will give immunity. Also a very small amount of unchanged *virus fixe* is given by the Hogyes dilution method. It is evident that the whole amount of *virus fixe* which is given in from eighteen to twenty-one days by the old scheme could be reduced to one or two injections with unchanged *virus fixe*.

What rôle the toxins play in the immunization I leave undecided. Their existence is not evident and in my opinion they are without great value for the immunization.

The experience with other vaccines has demonstrated that a certain percentage of cases, in spite of the same conditions, cannot be immunized or, better said, that the immunity cannot be produced to such a point that a complete protection is assured. We have also to count on a certain amount of failure, in spite of using the most intensive treatment.

100 East Stockton Avenue

# A CONSIDERATION OF SOME CHEMICAL TRANSFORMATIONS OF PROTEINS AND THEIR POSSIBLE BEARING ON PROBLEMS IN PATHOLOGY

FRANK P. UNDERHILL

NEW HAVEN, CONN.

Recent investigations concerning the structure of proteins have led to a readjustment of our ideas with respect to the manner in which these substances may become an integral part of the organism, and the study of the changes which occur from the time when protein has been built up into cell structure until its exit from the body in the form of waste products is at present only in its infancy. According to the newer conception, the protein molecule is a huge complex consisting of the union of a large number of simple amino-acids. This conception is due largely to the researches of Emil Fischer, who has succeeded in fastening together various combinations of amino-acids in such a manner that the resulting compound behaves in some respects like certain of the proteins. Some of these substances, called polypeptids, have indeed been isolated from the decomposition of native protein. According to Fischer, proteins are merely mixtures of complex polypeptids and cannot be considered as chemical individuals. This view, however, is not shared by other protein chemists.

In its passage through the alimentary canal the large protein complex undergoes a degradation,—a transformation into simpler molecules which are still regarded as simple proteins, together with a long chain of amino-acids belonging to the aliphatic, aromatic and heterocyclic series. Our modern view of the nature of protein forbids the acceptance of the older idea that the necessity for alimentary treatment of protein is merely to transform protein into a condition suitable for absorption. Obviously, solubility and diffusibility are only a small portion of the process, otherwise it would be unnecessary to entail so much labor on the gastro-enteric tract by the apparently needless formation of amino-acids. The need for nitrogenous substances is to replace cellular structures worn out through metabolic activities. Just how this replacement occurs is problematical. Certain it is that the only detectable nitrogenous food supply for such structures is to be found in the proteins of the blood. No amino-acids or other protein decomposition products have been isolated from the

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\* The Middleton Goldsmith Lecture for 1911 read before the New York Pathological Society at the Academy of Medicine March 18, 1911.



blood<sup>71, 2</sup> An explanation for the necessity for the extensive disintegration of the protein molecule has been offered as follows

"Every species of animal—in fact, every individual—has its specifically constituted tissues and cells. If the diet were always the same, the formation of the tissues might bear some close relation to the components of the food. The diet varies, however, and, especially in the case of human beings and the omnivora, is exceedingly diverse in nature and to make its organism independent of the outer world in the matter of food taken, it disintegrates the nutrient it receives, and utilizes those components which may be of service to it in building up new complexes."

Many important functions have been attributed to the intestinal wall, but perhaps none of more significance than a selective power for the synthesis of amino-acids into serum albumins. According to this view, the intestine receives a series of more or less simple amino-acids and by uniting them in varying proportions forms definite compounds, probably serum proteins, to meet the organism's requirements. The serum proteins are then drawn on to furnish nitrogen requirements for the specific organ or group of cells. This probably entails a further transformation. Such a theory accounts for the necessity of the complete degradation of protein in the gastro-enteric canal and accords with the entire absence of cleavage products in the blood. On the other hand, this extensive degradation, synthesis and further disintegration appears quite uneconomical physiologically. In the first place, only a comparatively small amount of nitrogen is needed to rebuild tissue, and the excess must be transformed into some form easy of elimination, all of which entails loss of energy and tissue waste. It is a matter of common observation that when protein is fed, practically all the nitrogen is rapidly excreted, and one is inclined strongly to believe that this portion has never been re-synthesized into protein. If amino-acids or other decomposition products could be found in the blood, the solution of the problem would be at hand. The failure to discover them does not disprove their presence, however, since the quantity in the portal vein, at any one moment, may be so small as to escape detection with our present methods.

Whichever way one views this problem, the fact remains that sooner or later intermediary processes must be concerned, primarily with a series of amino-acids. These are the substances that must be metabolized in either case, and it is to some of the transformations that these compounds may undergo within the organism that I particularly desire to call attention. It is my purpose to indicate the possible bearing of certain types of intermediary processes upon problems in pathology, for it is my belief that the hope for a complete understanding of some of the phases of disease will be realized in proportion as our knowledge of intermediary processes increases.

## DEAMINATION AND THE SIGNIFICANCE OF AMMONIA IN THE BODY

Modern investigations teach that when amino-acids obtain entrance to the tissues, a process of deamination rapidly occurs, the nitrogen is split off in the form of ammonia. In other words, the amino-acid is converted into a nitrogenous and a non-nitrogenous portion. It is probable that this process of deamination takes place for the most part in the liver, although the liver is by no means the only organ capable of performing this reaction, as has been pointed out by Jacoby<sup>51</sup> and Lang<sup>57</sup>. The older observation of Nenki, that blood flowing from the intestine is richer in ammonia than the blood of any other vessel, may also be regarded as probably our first indication that the intestinal wall may carry out the process of deamination. Ordinarily, the ammonia split off reappears in the urine as urea, being synthesized into this closely related compound in the liver. That deamination occurs also with certain protein complexes, has been conclusively demonstrated by Cohnheim<sup>24</sup>. The further transformation of the non-nitrogenous part will be considered later.

Under normal conditions the quantity of ammonia excreted in the urine varies within certain well defined limits, and in general is directly proportional to the intake and total output of nitrogen. The elimination of ammonia in disease may vary enormously, and usually when a changed excretion is observed it is in the direction of a greatly increased output. In fact, ammonia output in the urine is probably more easily affected than the elimination of any other single urinary constituent, except the excretion of urea which bears a reciprocal relation to ammonia. If the literature relating to ammonia output in disease is reviewed, it is found that increased ammonia excretion<sup>77</sup> is characteristic of pathological conditions apparently widely diverse in nature. For instance, an augmented ammonia output has been observed in cholera, intestinal hepatitis, carcinoma of the liver, cirrhosis of the liver, pneumonia, polyarthritis, typhoid, various other fevers, acute uremia, phosphorus poisoning, gastro-enteritis, starvation, diabetes, pernicious vomiting of pregnancy, eclampsia, etc.

Ammonia in the normal urine is looked on to-day as an index to the quantity of acids present. Acids are toxic to the organism, as has been demonstrated repeatedly, and ammonia is diverted from its transformation into urea to neutralize these acid radicles<sup>42, 44, 25, 31, 52</sup>. The same idea prevails with respect to diseased conditions in which increased ammonia in the blood and urine is regarded as evidence of increased production of acid radicles<sup>77</sup>. It is a well-known observation that this excessive elimination may be greatly diminished by feeding other alkalis, as, for instance, in diabetes. If ammonia is employed in the tissues merely to neutralize acid radicles, it would seem fair to assume that if

sufficient alkali were introduced, no ammonia should appear in the urine. Experimentally, such a condition has never been brought about in spite of very large doses of alkali. From this fact it would appear that a certain quantity of ammonia is continually present in the blood. This holds true also for the herbivora, even though these animals are assumed to neutralize acid radicals by alkalies other than ammonia.

Throughout the literature relating to acidosis and ammonia excretion in the urine, emphasis is laid on acid radicals as toxic agents. Little or no attention has been devoted to the rôle which may be played by ammonia itself when viewed from the same standpoint. As a matter of fact, ammonia is exceedingly poisonous and few salts exceed those of the ammonium series in comparative toxicity. On the other hand, of the acid radicals which are supposed to exert such deleterious effects, as, for example, in diabetes, not one has been shown to have any strikingly toxic properties at least in the normal organism. From these statements the possibility is offered that increased ammonia output in the urine may really mean increased ammonia production resulting from decreased urea formation. Experimentally, there is no evidence that such may not be the case, and according to this view ammonia must be neutralized, which would account for the presence of organic acids in the urine, as in diabetes, starvation, liver disorders, etc., precisely as the introduction of camphor, menthol, thymol, etc., accounts for the appearance of glycuronic acid in the urine. In this connection another interesting problem presents itself. In diabetes, beta-oxybutyric acid is the acid formed in large quantity, whereas in other conditions, as in cirrhosis of the liver, lactic acid is found. As a rule, the two do not occur together except in starvation and in pathological conditions in which inanition is an accompaniment. The presence of these two compounds in the urine would indicate two different types of mechanism slightly diverted from the normal.<sup>23</sup> In entire accord with the theory that ammonia may be the toxic agent are the observations of Carlson<sup>21</sup> and Jacobson.<sup>19</sup> The former has shown an increased quantity of ammonia in the blood after complete thyroidectomy and parathyroidectomy. The latter has demonstrated that the concentration of ammonia in the blood necessary to produce experimental ammonia tetany is practically equal to that found during parathyroid tetany. "This supports the view that the increased ammonia in the blood of parathyroidectomized animals is directly responsible for the tetany and the depressive symptoms."<sup>19</sup>

If, on the assumption that a common law underlies all the various pathological conditions mentioned, one attempts to account for the presence of ammonia in the urine, the suggestion presents itself that it is in some way connected with the metabolism of the carbohydrates. In practically every condition in which ammonia in the urine is characteristic,

there is either a lack of carbohydrates, as in prolonged starvation, or a faulty utilization of carbohydrate, as in diabetes, cirrhosis of the liver, or after complete removal of the thyroids and parathyroids, etc.<sup>92</sup> It would appear, therefore that carbohydrate is the factor controlling the regulation of ammonia production.<sup>93</sup> Thus in prolonged starvation, ammonia in the urine may be greatly diminished by feeding carbohydrate.<sup>77, 93</sup> In the solution of the problem as to the part played by carbohydrate, at least two possibilities are presented. 1. Carbohydrate influences the output of ammonia indirectly by its effect on the combustion of fat, for it is well known that fat is burned much more readily when carbohydrate is present than when the store of this substance in the body is greatly depleted. 2. It may be possible that the liver cell, for instance, is incapable of effecting urea synthesis in the presence of insufficient carbohydrate in that organ. The latter hypothesis certainly presents interesting problems, both for the physiologist and for the pathologist. Attempts have been made in our laboratory to follow this hypothesis to its logical conclusion. The results thus far obtained, however, have not been far-reaching for the reason that it is exceedingly difficult to obtain the proper experimental conditions. The investigation has been carried out on animals entirely. In the first place, an endeavor has been made to remove the carbohydrate store from the animal's body by various means with the hope of inducing increased ammonia in the urine. Prolonged starvation, phosphorus poisoning, a combination of the two, phloridzin intoxication alone and together with prolonged inanition, and cocaine poisoning have proved unsuccessful in inducing increased output of ammonia. This result is in harmony with those obtained by other investigators (Jackson and Pearce,<sup>48</sup> Richards and Wallace,<sup>83</sup> Underhill and Kleiner<sup>94</sup>). These facts by no means invalidate the hypothesis, for it is well known from the researches of Pflüger and his pupils that it is exceedingly difficult to get dogs glycogen-free. Since it is well known that dogs are refractory in this respect, inanition experiments were carried out also with the pig and rat, omnivora, and hence, presumably, allied to man in metabolism. The results were in entire accord with those with the dog. Ammonia in the urine was not increased. From this point of view it seems most probable that the decision of this question can be obtained most readily with the human subject.

If ammonia is to be regarded merely as an alkali for neutralization purposes, rather than as a toxic agent *per se*, it may be cited as a splendid illustration of the "factor of safety" principle enunciated by Meltzer<sup>97</sup> for other mechanisms. Ordinarily, ammonia is transformed to urea, but if acid radicals are floating in the body fluids they are rendered inert by union with ammonia, hence less urea is formed. Therefore, increased ammonia in the urine, with a corresponding diminution in the urea may

be regarded as an indication that the body is endeavoring to maintain normal conditions and not that there is necessarily any inability to form urea on the part of the organism, or that lesions in one or another organ are necessarily related to increased ammonia output. Indeed, even when acute yellow atrophy of the liver is at its height, the quantity of ammonia in the urine may be normal.<sup>77</sup>

Closely associated with problems concerning the significance of ammonia are those having to do with the relation of this substance to the amino-acids and the mechanism of deamination. Within the last few years discussion of the relation of so-called defective or insufficient deamination in a series of pathological conditions has come into vogue. It has been assumed that the liver was incapable of performing its function and that the condition was indicated by high ammonia and a high undetermined nitrogen in the urine. It does not seem to have occurred to those who advocate this point of view that high ammonia and the presence of amino-acids in the urine present incongruous conceptions if the sum of urea and ammonia nitrogen is normal. In other words, if deamination were defective, one would expect low ammonia in the urine when amino-acids are present. Much stress has been laid latterly on the occurrence of amino-acids in the urine. In health a little glycocoll has been isolated in the urine which is not strange when one considers the rôle of glycocoll as a compound intended to render toxic substances innocuous as in the case of benzoic acid and the comparative difficulty with which glycocoll is burned. Leucin and tyrosin have been isolated from the urine of patients with acute yellow atrophy, and with phosphorus poisoning.<sup>78</sup>

According to Ignatowski,<sup>47, 4, 33, 34, 104, 88, 11, 65, 78</sup> glycocoll, leucin, tyrosin and aspartic acid are found in pneumonia and leukemia. Similar finds are obtained in scarlatina and typhoid.<sup>50, 39</sup> Insults to the pancreas<sup>17</sup> may lead to the excretion of a polypeptid which on hydrolysis yields tyrosin, and according to several observers<sup>70, 2</sup> a similar compound may be obtained from diabetic urines. As a result of disturbed metabolism induced by lack of oxygen,<sup>61, 62</sup> amino-acids may appear in the urine as well as after ether-chloroform narcosis.<sup>5</sup> These bodies may also be present in exudates and in the fluids formed in edema.<sup>70, 75</sup>

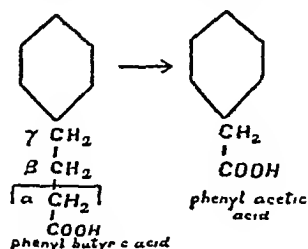
To account for the presence of amino-acids in the blood and hence also their excretion by the kidney, it is unnecessary to assume that defective deamination is responsible. They may be produced, as for example, by increased autolysis of a tissue or organ in a part of the body far remote from the organ or organs possessing the power of deamination and may therefore be eliminated through the urine before the organs of deamination have had an opportunity of performing their function. In other words, these compounds may be formed in the muscles, for instance, and be eliminated in a large part by the kidney before the liver, which may be

cited as an organ of deamination, has had an opportunity of acting on them. In harmony with this idea may be cited the conditions which obtain in this respect in cystinuria.<sup>75</sup> In certain of these patients, the amino-acid, cystin, is eliminated through the urine either alone or in company with other amino-acids, for example, leucin and tyrosin. Apparently, the cystinuric patient is incapable of deaminating and burning the cystin. Nevertheless, when cystin<sup>11, 102</sup> is fed to such individuals they experience no difficulty in completely deaminating and burning this amino-acid, and it has also been demonstrated that certain, at least of the cystinurics, can handle other amino-acids, as tyrosin<sup>90</sup> and aspartic acid,<sup>103</sup> when fed. The reason for the presence of amino-acids in the urine under the pathological conditions previously cited, may be similar to that frequently given for cystinuria, namely, that the cystin eliminated arises as a result of processes within the organism, not necessarily from the food. And in neither case is it necessary to assume defective deamination.

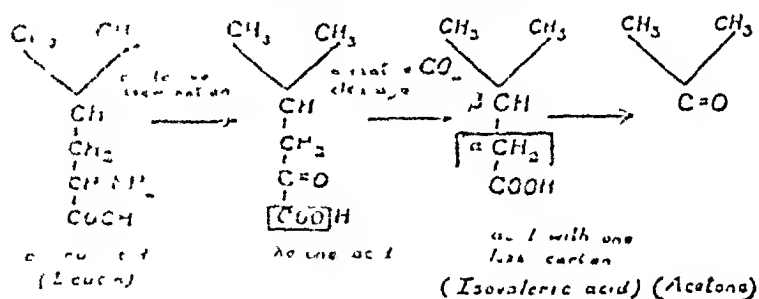
#### THE FURTHER FATE OF AMINO-ACIDS

Until recently our knowledge concerning the exact mode of decomposition of the cleavage products of protein has been extremely limited. It has been assumed for years that the non-nitrogenous portion of the amino-acid is oxidized and hence may be looked on either as a direct source of energy, or as potential energy residing in carbohydrates or fats synthesized from such material. Recent observations, however, have tended to give us a more enlightened view as to the exact way in which these amino-acids are handled. Thus, from the investigations of Emden, Salomon and Schmidt,<sup>55</sup> it may be seen that leucin added to the blood of a dog and made to pass through the surviving liver causes a considerable increase in the acetone contained in the circulating blood. Under normal conditions some acetone is a product of liver activity.<sup>53</sup>

In order to understand the steps necessary for the production of acetone from leucin, certain other facts must be taken into consideration. Knoop<sup>53</sup> has conclusively demonstrated that the aromatic fatty acids are decomposed in the body in such way that there is an oxidation at the beta carbon atom followed by a cleavage in the side chain between the alpha and beta carbon atoms. Thus, phenylbutyric acid is decomposed into acetic acid and phenylacetic acid. The latter appears in the urine, and the acetic acid is presumably decomposed to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ .

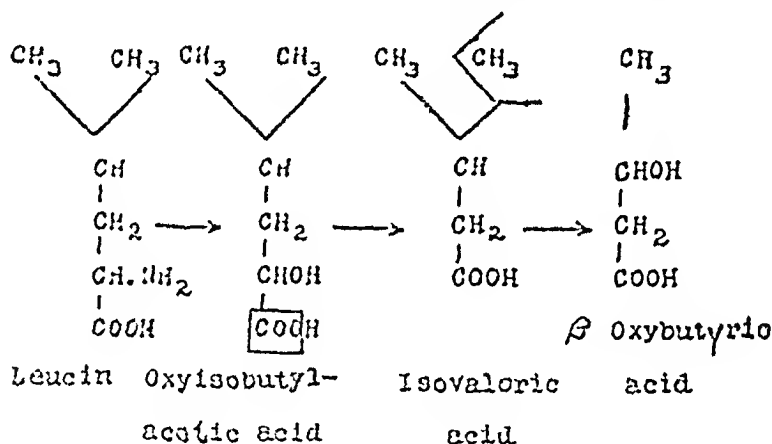


It is perfectly possible that the breaking down of the aliphatic fatty acids takes place in somewhat the same fashion. Reasoning from this viewpoint it is probable that the transformations which occur in the production of acetone from leucin are as follows:



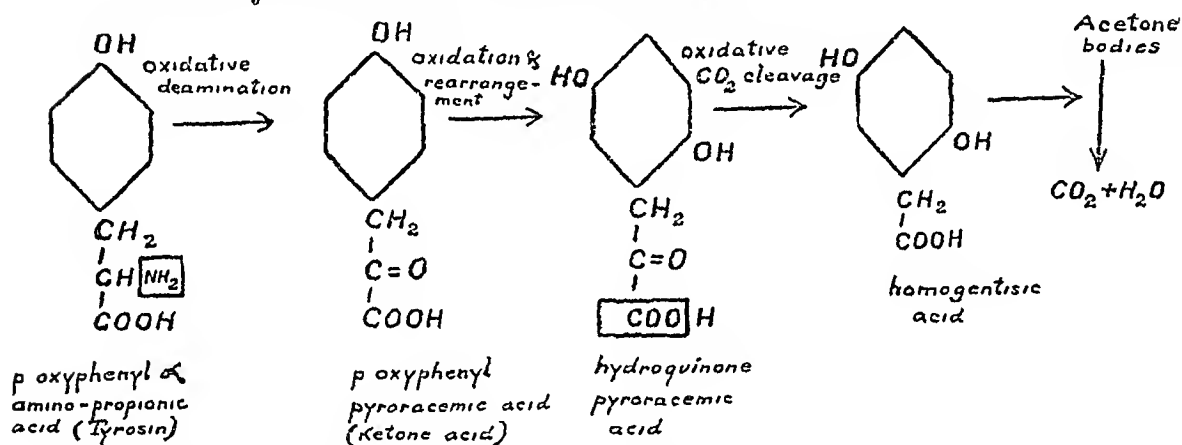
Leucin first undergoes oxidative deamination by which a ketone acid is formed. Then by oxidative  $\text{CO}_2$  cleavage isovaleric acid is produced. Next cleavage takes place between the alpha and beta carbon atoms.

On the other hand, Baer and Blum<sup>12</sup> have found an increased output of beta oxybutyric acid in the urine after giving leucin to a diabetic and the following transformations have been attributed to it:

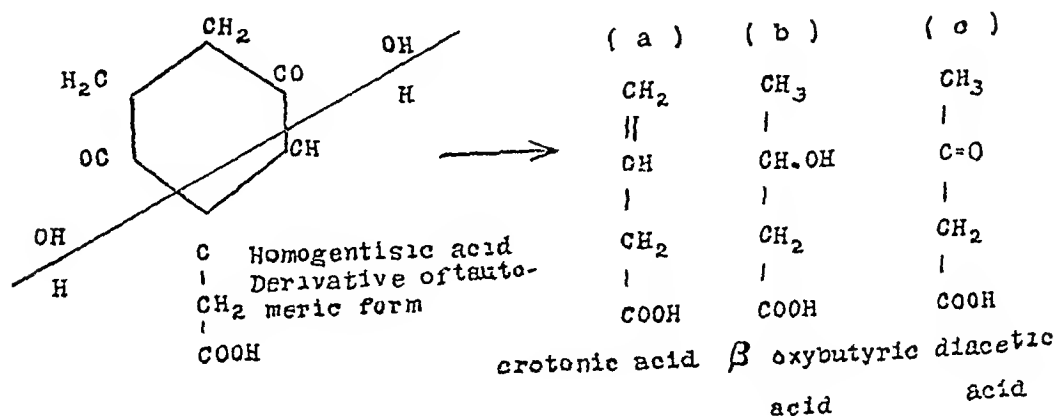


Whether one can assume from these observations that the organism of the diabetic is incapable of handling the amino-acid in a normal manner remains a problem for future investigation to decide. "With the proof of acetone formation from products obtained from protein derivatives, we obtain for the first time a clear idea concerning the utilization of the carbon chains free from nitrogen from certain amino-acids. We learn in this way to consider the formation of acetone as a normal process, it being a normal product in the decomposition of leucin."<sup>13</sup> If acetone is a step in the demolition of certain of the amino-acids, why is it that in various pathological conditions, as diabetes, gastro-enteritis, starvation, etc., large quantities of this substance are excreted in the urine instead of being further decomposed as in health? In answer to this query, it may be stated that probably only a small portion of the acetone excreted under the conditions just cited really has an origin in the carbon-free rest of the amino-acids.

When a fatty acid attached to the benzene ring is followed through the organism, the changes which occur are not quite so simple<sup>1, 26</sup> Ordinarily, when fed to the normal organism, tyrosin, which is such a combination, entirely fails of detection in the excreta Not only has the fatty acid been decomposed, but the benzene ring has been broken, which may be regarded as a difficult chemical reaction The possible steps through which tyrosin must be carried have been indicated by Neubauer<sup>74</sup> There is a class of pathological subjects that present certain anomalies in metabolism These subjects, alkaptonurics, excrete urine containing homogentisic acid<sup>75</sup> For a long time it has been recognized that tyrosin fed to the alkaptonuric results in an increased output of homogentisic acid Ordinarily, this substance is decomposed in the organism, but in the class of individuals referred to, it would appear that this decomposition is withheld or inhibited The changes which lead to the formation of homogentisic acid in the alkaptonuric and hence probably also in the normal subject have been outlined as follows



In harmony with the idea that homogentisic acid is an intermediary product in the decomposition of tyrosin is the demonstration that the normal liver is capable of forming acetone from homogentisic acid<sup>35</sup> The reactions which occur are probably in accord with the suggestion given below





So far as the condition of alkaptonuria itself is concerned it can hardly be looked on as distinctly a pathological state, it is rather an anomaly of metabolism. Nevertheless, it is possible that it may bear a relation to disease. Thus it has been suggested that there is an as yet unexplained relationship between alkaptonuria and chronic polyarthritis.<sup>22, 23, 24, 25</sup> Homogentisic acid is also closely related to certain pigments which occur under abnormal conditions. It may be easily transformed into a dark-colored pigment which bears a relation to the group of bodies known as melamins which are also protein derivatives. Whether homogentisic acid is concerned in the production of color in melanotic tumors remains a question for future decision. It has been suggested<sup>26</sup> that there is relationship between homogentisic acid and the coloring of the bones in ochronosis and at times ochronosis and alkaptonuria occur simultaneously.<sup>27</sup>

If it can be demonstrated that alkaptonuria bears a direct relationship to certain diseases it is obvious that the complete understanding of the chemical transformations which lead to the production of this anomaly will undoubtedly prove of value in the unraveling of other abnormal processes.

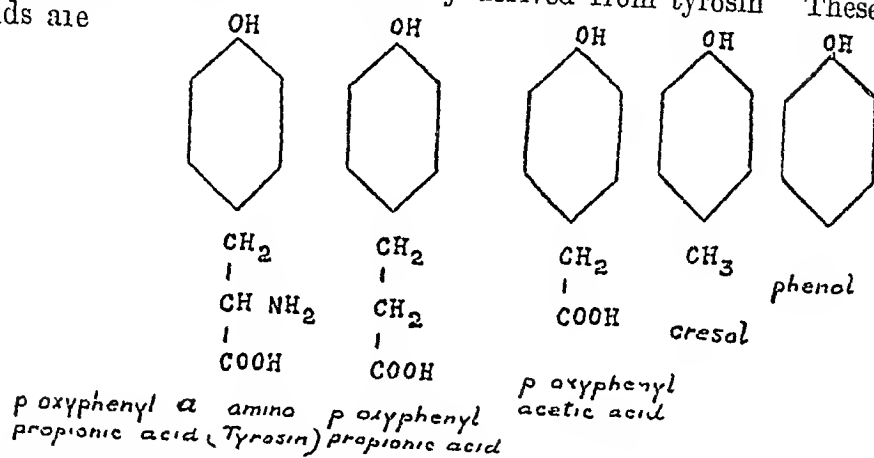
According to the views which have just been expressed concerning the fate of amino-acids in the body, the non-nitrogenous portion is merely broken down into simpler compounds and eliminated. This process of degradation undoubtedly furnishes a certain amount of energy in the form of heat. Looked at from another point of view,<sup>28</sup> the non-nitrogenous part of certain, at least, of the amino-acids may be synthesized to carbohydrate and fat which in turn are utilized as sources of energy.

Thus far, the whole question as to the fate of amino-acids in the body has been looked on as one of analysis or demolition. Recently it has been suggested that there may be a synthesis of amino-acids within the organism, and Knoop<sup>29</sup> has placed on record certain experiments which tend to substantiate this view. Thus, after feeding phenyl ketonebutyric acid or even oxyacids of a similar type, he was able to separate from the urine an acetyl derivative of an amino-acid. Here, for the first time, there is established a direct relationship between protein and carbohydrate metabolism.

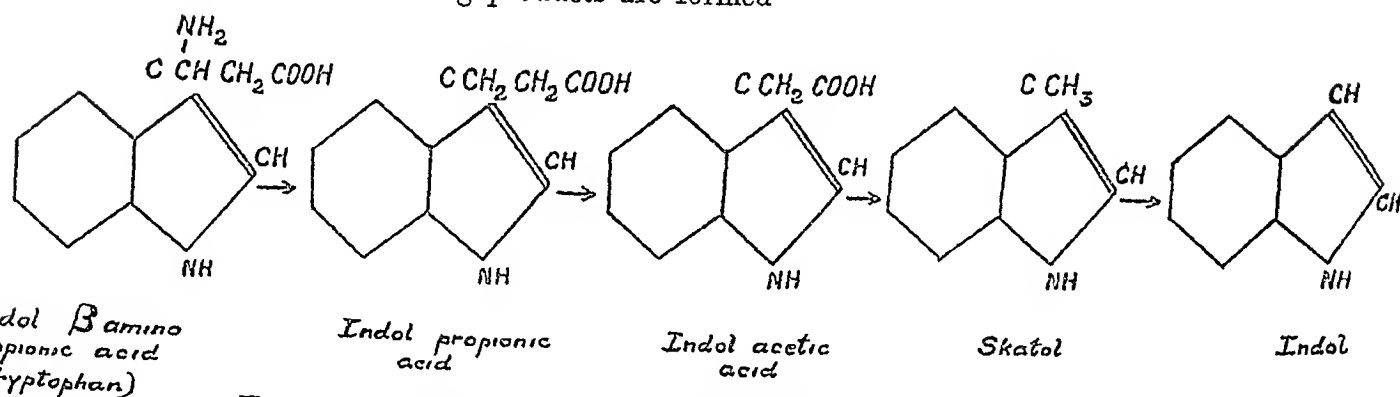
#### BACTERIAL PRODUCTS

*Indol, Skatol, etc*—As a result of the bacterial digestion of protein, certain well-known and well-defined products have been isolated and their specific influence on the organism noted. Not only have these bodies been separated and identified but the chemical transformations leading to their formation have been made clear. The protein derivatives, tyrosin and tryptophan, are the mother substances for the best-known bacterial products. In the intestinal contents have been found a number

of substances which are undoubtedly derived from tyrosin These compounds are



According to these reactions, a deamination of the aromatic amino-acid must occur in the large intestine. The further reaction for the production of p-oxyphehylacetic acid involves the cleavage of carbon dioxid from the carboxylic group and subsequent oxidation of the carbon atom. If phenol is produced from cresol, then demethylation must occur. These reactions if correct, must involve the processes of deamination, cleavage of carbon dioxid, oxidation and demethylation. From tryptophan the following products are formed

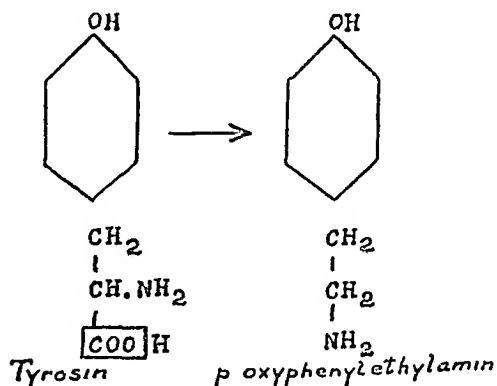


From these reactions it is obvious that the same chemical changes have occurred as in the transformations for tyrosin, namely, deamination, carbon dioxid cleavage, oxidation and finally demethylation. On the other hand, it has been suggested recently that indol may arise in part as a result of intermediary processes quite distinct from those involved in putrefaction.<sup>16</sup>

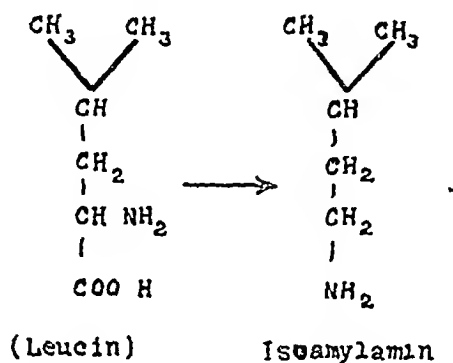
Ordinarily, when intestinal putrefaction is mentioned one invariably thinks of indol and skatol as being responsible for the series of disturbances which may be associated with this condition. It has been assumed that a long list of pathological conditions may be closely related to increased intestinal putrefaction. Thus, this condition has been held responsible in part for sciatica, tetany, epilepsy, eclampsia, many forms of dermatitis, cirrhosis, arteriosclerosis, various types of nervous diseases, chlorosis, myxedema, cretinism, pernicious anemia and nephritis.<sup>98, 73</sup>

Although there is abundant clinical evidence that excessive intestinal putrefaction may be associated with or responsible for marked disturbances, the substances thus far isolated from intestinal contents can not be said to possess very profound toxicity. It is true that indol when administered in quantities up to 2 gm per day causes frontal headache, irritability, insomnia and confusion<sup>45</sup> and it has been shown further that indol and skatol cause muscle to react to stimuli like fatigued muscles<sup>46</sup>. But the comparatively slight toxicity can hardly be responsible for some of the symptoms observed. Various explanations have been offered to account for the discrepancy noted between clinical evidence of intestinal intoxication and the fact that the substances formed thus far isolated are only slightly toxic. The most plausible explanation for the discrepancy mentioned is that the list of compounds which may be formed in putrefaction has not yet been exhausted and it is possible, and indeed probable, that in time other compounds of putrefactive origin will be found that will adequately account for the clinical symptoms observed. On the other hand, it be possible that indol and skatol may exert quite different effects on the normal organism from those which it exerts on a body whose resistant powers have been lowered as a result of other pathological processes. In other words, the receptive condition of the body under the two conditions mentioned may be entirely different, producing in turn quite radically differing symptoms.

*Amines and Their Formation*<sup>13</sup>—That we have by no means isolated all the active principles from putrefactive mixtures may be well illustrated by the investigations recorded during the last three years. In 1907 Dixon and Taylor<sup>29</sup> aroused considerable interest by the publication of their observation that alcoholic extracts of the human placenta when injected intravenously caused a marked rise in blood-pressure and contractions of the pregnant uterus. On repetition of this work, Rosenheim<sup>87</sup> failed to corroborate the findings of Dixon and Taylor when extracts of perfectly fresh placentas were employed. When, however, extracts of placentas in various stages of putrefaction were intravenously administered, results were obtained identical with those of Dixon and Taylor. A substance responsible for these effects has been separated and identified by Baiger and Walpole,<sup>15</sup> according to whom the active principle is *p*-oxyphenylethylamin and may be derived from tyrosin as a result of the following reaction

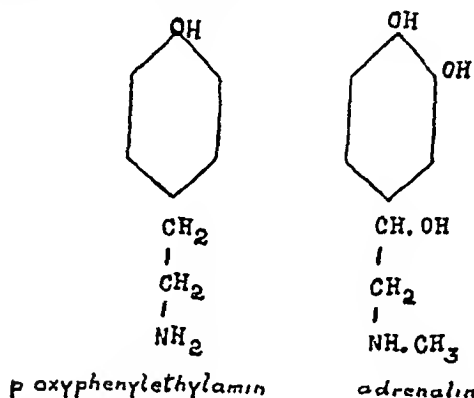


Moreover, iso-amylamin has been isolated from putrefactive mixtures probably being derived from leucin in accordance with the following reaction



These results have led the authors to remark that they are induced "to emphasize the probability that the amins which we have isolated are normally formed by putrefaction in the intestine and are absorbed from it"<sup>15</sup>

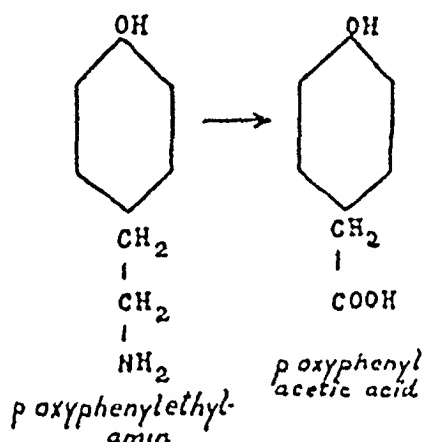
The compound, p oxyphenylethylamin, is of peculiar interest for several reasons. In the first place, it was originally isolated by Emerson<sup>36</sup> from an autolysis of pancreas and its mode of formation from tyrosin has always been considered unique. It is obvious at present that it was probably produced by putrefaction in this case also. Much more interest attaches to this substance from its great resemblance, both structurally and pharmacologically, to epinephrin



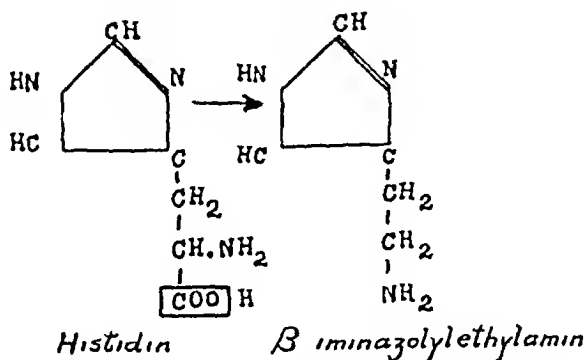
"P oxyphenylethylamin has an action very similar to that of adrenalin [epinephrin], reproducing both the motor and inhibitory effects of nerves of the true sympathetic system. It produces the motor more powerfully than the inhibitory effects. Its action differs from that of adrenalin in being weaker, and slower in onset, and in being less strictly though mainly peripheral. It is absorbed from the subcutaneous tissues and the alimentary canal and produces its effects when so administered."<sup>27</sup> Isoamylamin has a similar action.

Finally, it is of exceeding great interest to note that p oxyphenylethylamin is one of the substances which give to ergot<sup>14</sup> its characteristic

action on the uterus. It is also probable that it is identical with the urohypertensin of Abelous and Baudier.<sup>26</sup> These observations also indicate the necessity for controlling all possible sources of bacterial contamination when extracts of animal tissues are employed in demonstration of specific action. Again "Many observations have been published recently concerning the presence in the blood-serum and urine in various pathological conditions, of substances which cause dilatation of the pupil of the enucleated eye of the frog. The fact that both these amines have this action casts some doubt at least on the validity of the assumption made by certain observers, that the substance in serum, responsible for this effect is adrenalin."<sup>27</sup> On introduction into the body, the base is eliminated as *p*-oxyphenylacetic acid,<sup>28</sup> another example of deamination.



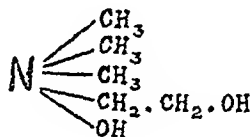
When histidin is subjected to the action of putrefactive bacteria, a compound<sup>7</sup> is produced which holds promise of being responsible in a measure for certain reactions which have long been unexplained.



This substance, beta-iminazolyethylamine, resembles in some respects *p*-oxyphenylethylamine in that both compounds are contained in ergot extracts, and both substances exert similar influences on the muscle of the uterus. In addition to the reactions possessed in common with *p*-oxyphenylethylamine, beta-iminazolyethylamine is capable of calling forth symptoms practically identical with those induced by injections of peptone solutions, or by serum or other protein in the sensitized guinea-pig, that is, producing anaphylactic shock.<sup>27</sup> The base has also a mild,

direct, stimulant effect on the activity of the salivary glands and the pancreas. This secretory action, being paralyzed by atropin, may be regarded as a weak action of the pilocarpin type, the association has some interest in that pilocarpin also contains an iminazole ring. More recently this base<sup>28</sup> has been isolated from extracts of the intestines, thus lending support to the suggestion that under normal conditions it may exert a more or less definite function in the maintenance of nutritional rhythm.

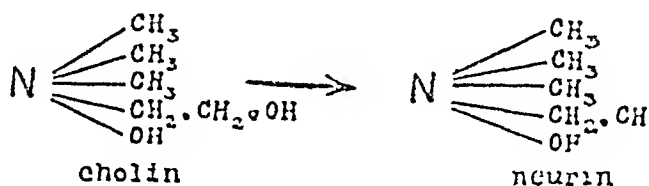
Closely associated with *p*-oxyphenylethylamin in extracts of placentas is another compound which may also be considered as an amin and which has an action antagonistic to that of *p*-oxyphenylethylamin. This compound, cholin, has been the subject of a great deal of discussion during



the last few years. It undoubtedly has its origin in a lipid compound, lecithin, a constituent of practically all cells. It is, therefore, apparent that in putrefactive processes in the tissues, cholin may arise in relatively large quantity and, although not highly toxic when given by mouth, it may be exceedingly poisonous when allowed to come in contact with nervous tissue. Thus, Donath<sup>30</sup> observed severe tonic and clonic convulsions after cholin had been injected directly into the cortex or under the dura. This investigator offers the opinion that cholin may be responsible for epileptic convulsions—an opinion founded on the fact that he with other investigators<sup>43, 86</sup> has been able to demonstrate the presence of cholin in large quantities in the cerebrospinal fluid of epileptics and in other conditions associated with destruction of nervous tissue. In accordance with this idea, unsuccessful attempts<sup>95</sup> have been made to demonstrate the presence in the blood of cholin in animals during the tetanic convulsions caused by complete removal of thyroids and parathyroids. The removal of the glands has been shown to result in marked changes in certain areas of the nervous system,<sup>97</sup> and it was assumed that these histological changes were due to chemical reactions whereby cholin might be liberated and produce a secondary effect.

Chemically related to cholin is neurin, a substance easily formed from cholin by oxidation, which is nearly twenty times as toxic as the latter. The possibility presents itself that neurin may be formed from cholin within the organism under certain pathological conditions and may be responsible for some of the symptoms characteristic of certain abnormal conditions as salivation, vomiting, diarrhea and a specific action in causing arrest of respiration. This formation of neurin within the organism and any relationship which it may bear to deranged metabolism has never

been conclusively demonstrated. It has been shown, however, that neurin may be excreted, at times at least, through the urine.<sup>50</sup>



These compounds together with muscarin and betain, constitute one of the groups of the ptomaines, so-called, and hence heretofore have been interesting chiefly because of their advent into the organism through the introduction of decomposing tissue taken as food. Nevertheless, inasmuch as they arise outside the body as a result of putrefactive process, there remains open the possibility that they may be formed in the alimentary canal or in tissues either in a process of degeneration or putrefaction. The old idea that there is a hard-and-fast line to be drawn between plant alkaloids and animal poisons is rapidly disappearing, and the fact that one toxic compound as for instance muscarin, occurs as a rule in plant tissue does not exclude the possibility of the presence of the same body as a result of chemical reactions within the animal organism. The best recognition of this disappearing demarcation line is to be found in the new publication by Wintcistem and Tiner,<sup>101</sup> where all basic substances, whether of animal or plant origin, are considered as alkaloids.

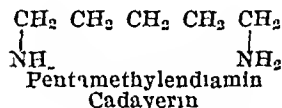
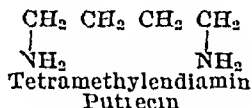
From this review of the more recently discovered compounds which may arise within the body by putrefactive processes, one fact stands forth with striking clearness, namely, the possible functions which some of these substances may exert in physiological processes and their significance in problems concerned with disease. We have seen that one compound resembles epinephrin, both structurally and in physiological activity, while another stimulates the activity called forth by pilocarpin. Epinephrin and pilocarpin are in daily use as drugs, the degree of whose activities may be regulated at will. The protein derivatives mentioned have practically similar actions but, as they arise within the organism, can not be subjected to voluntary control. It is likely that under normal conditions, only small quantities of these compounds may be thrown into the blood-stream and that there is some nice adjustment of mechanism which may have an influence on the further beneficial disposition of these bodies. It is conceivable, however, that at times an undue quantity of such material may overwhelm the regulating mechanism to such a degree that substances which perhaps normally aid in the maintenance of physiological rhythm may indeed become responsible for the advent of abnormal reactions. The suggestion is therefore offered that some of the disturbances associated with excessive intestinal putrefaction may have such an origin. A hypothesis of this sort readily furnishes an explanation for the vaguely

defined headache and general malaise characteristic of the previously mentioned pathological states

#### DIAMINES

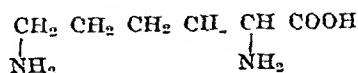
Cystinuria has been given a great deal of consideration by investigators for the excellent opportunity it afforded of elucidating some of the complex processes underlying the principles of intermediary metabolism. It has been and still is a matter of great uncertainty as to the origin and significance of cystin and the diamines, putrescin and cadaverin, which appear in the excretia of certain individuals. The appearance of cystin has been the subject of such widespread interest, and the results of study of cystinuria have been so extensive and are so well known that further discussion of this subject in this place appears superfluous.<sup>75</sup>

On the other hand, the diamines have not received so much attention. The structure of these bases is as follows:

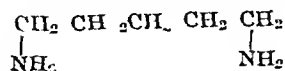


A third diamine, neuvidin or saprin, is isomeric with cadaverin. The diamines are eliminated, not only in the urine but also in the feces. As has been stated previously, they are found usually associated with cystin, although the condition responsible for the appearance of cystin in the urine does not seem necessary for the condition of diaminuria, for these substances have also been eliminated under certain other pathological conditions, principally, intestinal disturbances, as for instance, in various infections, in cholera,<sup>85</sup> dysentery, gastro-enteritis,<sup>84</sup> and from one case of pernicious anemia tetramethyldiamin was isolated.<sup>46</sup> The origin of these bodies appears to be in two diamino-acids that are products of normal digestion.

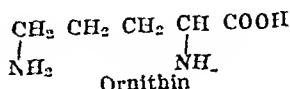
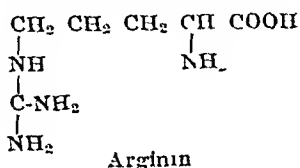
From lysin, which has the following formula:



CO<sub>2</sub> is split off, forming cadaverin, with the following formula:

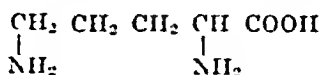


Putrescin is derived ultimately from arginin, guanidin and amino-valerianic acid. Kossel and Dakin<sup>55</sup> have demonstrated the existence of an enzyme, arginase, in certain tissues of the body which is capable of splitting arginin into urea and ornithin. Thus:

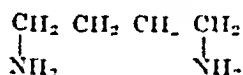




From ornithin, the formula for which is as follows



CO<sub>2</sub> is split off forming putrescin, the formula below



In intestinal disturbances, it is probable that these compounds are the result of the bacterial activity—indeed they may be the metabolic products eliminated by microorganisms. In cystinuria, however, it is possible that a different<sup>80</sup> explanation for diaminuria is pertinent. It may be assumed, for instance, that in the beginning cystinuria and diaminuria are brought about through a similar or indeed the same cause, or causes, for example, a gradually changing type of metabolism induced by some unknown agency, resulting in an anomaly of metabolism. If the anomaly is slight in character, cystin alone is eliminated as a result, whereas if the change in metabolism is sufficiently pronounced diamins are also excreted. If this assumption is accepted, it is easy to explain why in some cases of cystinuria the diamins are absent, and that gradually one or both of these compounds disappear, that cystinuria persists, but that cystinuria does not cease and leave diaminuria. Thus far all attempts to produce diaminuria experimentally have been unsuccessful. These bodies are possessed of a certain interest, aside from their chemical significance in that, like nearly all the amines, they are more or less toxic. It has been demonstrated experimentally that the diamins may also exert an influence on certain intermediary processes. Thus, according to Pohl,<sup>81</sup> feeding diamins inhibits certain well-known protective reactions which the organism is capable of putting forth, as for instance, the formation of glucuronates and the synthesis of hippuric acid.

The toxicity of these compounds calls to mind the poisonous action of another diamine, not found in the organism, namely, hydrazin,<sup>82</sup>



This substance is, however, very much more toxic than the diamins just mentioned. Its introduction into the organism is followed by marked histological changes<sup>83</sup> in various tissues, especially in the liver. In fact, the action of this substance is directed almost specifically on the liver, provoking fatty degeneration of that organ. Only the cytoplasm of the cell is attacked. Although the liver is almost completely transformed under the influence of hydrazin, no noticeable change in nitrogenous intermediary metabolism can be demonstrated through a study of the urinary constituents.

## APORRHEGMAS

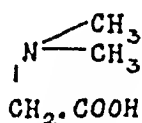
In a recent communication Ackermann and Kutscher<sup>8</sup> have proposed a new designation for the transformation products of amino-acids which are formed by life processes, whether in the animal or the vegetable kingdom. The term employed for these bodies is "aporrhegma." It is interesting to note the number of such compounds which may arise from putrefaction alone. The above-mentioned authors<sup>8, 9</sup> have given a list of these substances, together with the amino-acids from which they are derived.

AMINO-ACID	APORRHEGMA
Histidin	Iminazolyethylamin
Arginin	Iminazolpropionic acid
	Ornithin
	Tetramethylendiamin
Lysin	Aminovalerianic acid
Glutaminic acid	Pentamethylendiamin
Asparaginic acid	Aminobutyric acid
	Alanin
Glycocoll	Succinic acid
Leucin	Methylamin (?)
	Isoamylamin
	Isovalerianic acid
Picolin	Pyrolidin
Phenylalanin	Phenylethylamin
	Phenylacetic acid
	Phenylpropionic acid
Tyrosin	Oxyphenylethylamin
	Oxyphenylacetic acid
	Oxyphenylpropionic acid
Tryptophan	Indol
	Skatol
	Indolpropionic acid
	Indolacetic acid

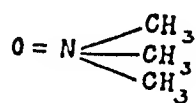
## METHYLATION IN THE ORGANISM

Until the last year or two, methylation within the organism was looked on as a reaction which occurred only rarely. With the exception of the well-known examples of the methylation of tellurium<sup>66</sup> and selenium, our knowledge of this type of physiological activity was exceedingly limited. Renewed interest in the process of methylation has been aroused by the recent investigations of Engeland,<sup>37</sup> who has demonstrated that complete methylation of most of the amino-acids derived from the protein molecule is far from a difficult reaction. The betains comprise all that group of bodies of the aliphatic series which are basic in character, thus, such compounds as the variousamins, cholin, muscarin, urea, creatin, etc. It is further probable that the wide-spread distribution of the betains, both in the animal and vegetable kingdoms, is to be explained solely by decomposition of protein. Moreover, it has been suggested that all the betains which arise from amino-acids formed by decomposition of protein bear a relation to the so-called "alkaloids."

A methylated amino-acid was unknown in the animal kingdom until completely methylated glycocoll was isolated in considerable quantity from crab meat<sup>8</sup> Accompanying methyl glycocoll was found trimethylamin oxid<sup>91</sup>

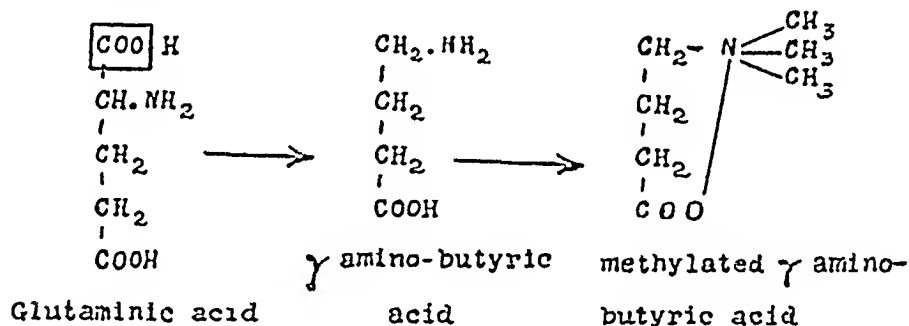


Methyl glycocoll

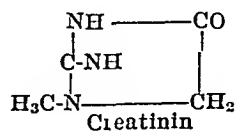
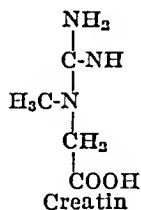
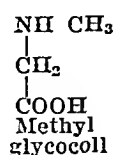
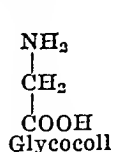


Trimethylamin oxid

Under normal conditions methylation of amino-acids does not occur to any considerable extent in the body of the warm-blooded animals, owing probably to the fact that if such compounds are formed, they are at once oxidized and serve as energy-producing material. When abnormal conditions are induced, however, as in phosphorus poisoning, where, perhaps, oxidative processes are less active the appearance of methylated compounds may be observed. Thus, the methylated gamma amino-butyric acid has been isolated recently from the urine of a dog poisoned with phosphorus<sup>38</sup>. This substance probably arises from glutamic acid, being transformed into gamma amino-butyric acid, then completely methylated and eliminated.



In plants and the lower animals methylated glycocoll is an amino-acid which is very widely distributed. Glycocoll is exceedingly resistant to decomposition by putrefaction, as was long ago demonstrated by Nencki. It is the only amino-acid which appears regularly in the urine, in the form of hippuric acid. It is found in its mono-methylated form as sarcosin combined with the guanidin residue, or modified urea rest, forming creatin of the muscle or creatinin of the urine of the higher animals.



*Creatin and Creatinin*<sup>68, 72</sup>—At present, perhaps the most interesting example of methylation may be found in the origin of the creatin of muscle and the creatinin of the urine. The exact significance of these

compounds is exceedingly obscure. It is known, for example, that under physiological conditions creatin is absent from the urine and that creatinin elimination is practically constant for a given individual. This elimination, however, is different for different individuals, but bears no relation to the volume of the urine or the total nitrogen excreted. From a long series of investigations, it has been concluded that creatinin is an index to some special form of normal metabolism, as yet unknown, but undoubtedly connected with processes concerned with muscle tissue. There is apparently a somewhat close relationship between muscle efficiency and creatinin elimination. Creatinin excretion varies greatly under abnormal conditions, being increased in fevers and diminished in a large number of other pathological states. Particularly striking is the diminution in excretion in abnormal metabolism of muscle tissue and of the liver.

Ordinarily, creatin is absent from the urine, but may be present in large quantities under certain pathological conditions, especially those associated with inanition, depression of liver function, or an abnormal state of muscle. The appearance of creatin in the urine under these circumstances might lead one to infer, by analogy with the presence of the betain of amino-butyric acid noted previously, that when abnormal processes are in order, certain chemical reactions are held in abeyance resulting in the elimination of creatin as an incompletely disintegrated intermediary product. From the most recent investigations<sup>22</sup> concerning creatin and creatinin, it appears likely that there is an intimate relationship between these substances and carbohydrate metabolism, although, at present, this relationship is not more than a mere indication. For example, creatin is present in the urine during fasting both in man and animals. Administration of carbohydrate under these circumstances causes the rapid disappearance of urinary creatin. It has also been suggested that one function of creatin being a base, is to serve as an alkali in the muscle to neutralize lactic acid which arises as a result of muscle activity.<sup>18</sup> Future investigations will, undoubtedly, reveal the significance of the interrelation of creatin, creatinin, muscle and carbohydrate and if the prophecy of Folin, uttered a few years ago before the Harvey society, comes true, the unraveling of this mystery will mean much in the domain of pathology.

#### THE PROTEOSES

Since the classic experiments of Schmidt-Muhlheim,<sup>20</sup> the behavior of the proteoses when injected into the blood stream has occupied the attention of a long series of investigators, the aim of whom has been to explain the significance of the reactions induced. It had been assumed for years previous to recent times that when proteoses were formed in digestion, they were absorbed into the portal vein, carried to the liver and there were detoxicated. As a matter of fact, it was also discovered

that proteoses introduced into the portal vein were incapable of provoking the typical effects induced by injection into the systemic circulation, an observation in entire accord with the then current views regarding the processes of digestion and absorption.

Renewed activity directed toward the solution of the problem concerning the normal presence of proteoses in the blood was awakened by the more recent investigations having to do with the degradation of the protein molecule in the enteric tract. According to one school, proteoses are absorbed into the blood, thus casting doubt on the prevalent idea that proteoses are broken into their simplest cleavage products, which are absorbed, and then further worked over into the needful compounds. Opposed to this theory is the school that is unable to find any evidence of proteoses in the blood normally. Amid these conflicting views and observations, the apparent consensus of opinion is that proteoses are absent from the blood under normal conditions.<sup>10</sup> Hence, when these substances are introduced into the blood-stream, they act as poisons calling forth certain characteristic reactions, fever, fall of pressure, changes in respiration, increased flow of lymph, saliva, and other secretions, but causing a somewhat prolonged anemia. There has been considerable controversy as to whether *pure* proteoses are really toxic. All the older observations were subjected to severe criticisms by Pick and Spiro<sup>80</sup> who maintained that proteoses as such are non-toxic and that the toxic principle is merely an adhering contamination, derived from the animal enzymes employed in the preparation of the proteoses. According to these authors, this substance, peptozyme, can be rendered non-toxic by subjecting the proteoses to a certain chemical treatment. Later observations,<sup>81</sup> however, have demonstrated that this conclusion is erroneous, since proteoses prepared from the action of vegetable enzymes on vegetable proteins and also naturally occurring vegetable proteoses induce the same train of symptoms as proteoses made from animal proteins and enzymes. Moreover, cleavage of proteoses beyond the biuret-yielding stage does not produce any symptoms. From the observations of Popielski, it is concluded that the substance responsible for the so-called proteose action may be removed in large measure by treatment with alcohol. This compound has been designated vasodilatin and, according to Popielski,<sup>82</sup> is not protein in nature. The fact, however, that this investigator has not succeeded in separating the vasodilatin from proteoses, together with the well-known fact that a portion of the proteoses are soluble in alcohol, militate against the correctness of the view that the proteoses action is separable from these bodies. On the other hand, it has been suggested<sup>38</sup> that a portion of the reactions provoked by "peptone" may be induced by the presence in the "peptone" of beta iminazolyethylamin which is capable of calling forth symptoms in nearly every respect similar to those produced by the "peptone." The single

exception noted is that beta iminazolyethylamin does not render the blood non-coagulable, which is distinctly characteristic for "peptone"

In our laboratory the observation has been made recently that the intravenous injection of proteoses produces a significant glycosuria. Coincident with the appearance of sugar in the urine, there is a marked hyperglycemia. The cause and possible significance of this reaction is being investigated. It appears a little strange that, of the long series of investigations carried out with the proteose injections, in not a single instance is there a recorded observation indicating glycosuria. When proteoses are injected into the blood-stream, the major portion of these compounds promptly reappears in the urine, although there is some evidence that they may be partially transformed into smaller molecules.<sup>23</sup> Albumosuria, so-called, is indicative of the formation of proteoses within the organism and is considered of importance in diagnosis. Thus, albumosuria may be observed in suppuration of all kinds, resolution of pneumonia, involution of the uterus, carcinoma, atrophy, eclampsia, leukemia, absorption of simple and inflammatory exudates, febrile conditions with destruction of tissue, and ulcerating pulmonary tuberculosis.<sup>100</sup>

It is possible, and indeed may be probable, that the proteoses formed within the body and thrown into the blood-stream may be responsible for some of the symptoms which are characteristic of some of the abnormal conditions cited. The fact that these substances are fairly toxic is almost evidence for the possibility just indicated. The significance of these compounds, both in physiology and pathology, warrants further investigation of the cause of the symptoms induced. It is hardly probable that any one specific group in these complex polypeptids is responsible for all the reactions noted and future study will undoubtedly demonstrate the presence of several distinct entities which specifically call forth certain symptoms.

The modern conception of the living cell makes enzymes responsible for the numerous types of known activities, thus we speak of enzymes facilitating reduction, oxidation, deamination, cleavage, etc. One organ is found to contain enzymes active to a high degree in one direction, another organ in another direction, and still a third organ which may furnish an almost unlimited number of enzymes capable of performing varied types of reactions. Ordinarily when enzymes are mentioned, one thinks involuntarily of the best-known agents, the digestive ferments. Our ideas concerning the exact mode of action of the enzymes that undoubtedly play an important rôle in intermediary metabolism are not well defined. It is probably, however, not an unwarranted position to assume that the several types of reactions discussed in previous portions of this paper have enzyme activity as their basis.

With the acceptance of enzyme activity as the foundation of cellular chemical activity, hence, intermediary processes, it is easy to conceive

how the induction of abnormal environment for these agents may lead to the production of distinctly pathological phases of metabolism with consequent injury to the whole physiological economy. In our endeavor to discover the reason, or the cause, for abnormal metabolism we have been led into the error of looking for changes of too great magnitude. Enzymes are exceedingly sensitive to all sorts of changes in environmental conditions. Too much acid, or too little, lack of the requisite inorganic salts, perhaps absence of carbohydrate—that group of substances vaguely designated as co-enzymes—may retard or hold in abeyance certain types of reaction the effects of which, over a considerable period of time, work injury to other types of enzymes until finally a large number of processes may be carried out only imperfectly.<sup>105</sup> Perhaps one of the best examples of the point under discussion may be taken from the recent work of Bywaters,<sup>9</sup> who found that the inverting power of an aqueous extract of yeast is increased ten- to fifteen-fold by the addition of acetic acid. On the other hand, this activity given by acid addition is susceptible of removal by alkalis, which subsequent addition of acid is capable of counteracting. Under one form of environment the power disappears and when changed to another the power is restored.

With data of this type at hand, is one unwarranted in suggesting the probability that pathological metabolism of various types may be the direct result of changed environmental conditions of intracellular enzymes? I believe that such a viewpoint will do much toward a solution of many problems concerning metabolism both from the standpoint of physiology and pathology, the dividing line of which is exceedingly narrow.

The advances of the future are to be made, I believe, by a careful study of small changes, details which at first thought perhaps appear insignificant but if followed will lead to far-reaching results. One of the best examples that can be cited in this connection may be taken from a recent paper on "The Influence of Alcohol on Nitrogenous Metabolism" by Mendel and Hilditch.<sup>106</sup> As a result of their study, the authors conclude that "the most significant impression, perhaps, which the analytical data afford, is the absence of *pronounced* alterations indicative of markedly disturbed protein metabolism." Emphasis on the words "absence of *pronounced* alteration" shows an entire appreciation of the presence of small differences. In this particular case, the organism was capable of using certain doses of alcohol to its distinct advantage, beyond this limit changes in purin output were observed. The cellular mechanism was altered in such a manner that certain types of processes were changed in a measure, the extent of the change being indicated by the altered purin output. The changed output was not large, but was it not just as good an indication of deranged metabolism as if the change had been twice as great? If the view suggested is correct, then the hope of future advances along the line of intermediary metabolism lies in an

appreciation of the significance of small differences and changes in the environmental conditions of the cell

445 Orange Street

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## STUDIES ON WATER-DRINKING

### VI THE ACTIVITY OF THE PANCREATIC FUNCTION UNDER THE INFLUENCE OF COPIOUS AND MODERATE WATER-DRINKING WITH MEALS \* 1

P B HAWK, PH D

URBANA, ILL

Numerous tests are in vogue clinically for the determination of the functional activity of the pancreas. The best known of these are the glutoid test of Sahli,<sup>2</sup> the nuclei test of Schmidt,<sup>3</sup> and the Cammidge<sup>4</sup> reaction, the last mentioned test having been rather more freely criticized than either of the others. Comparatively recently, clinicians have come to a fuller realization of the aid which a knowledge of the pancreatic enzyme concentration of the feces may give them in their diagnosis of pancreatic insufficiency. The accurate determination of the enzyme content of the feces under normal or pathological conditions is still, however, a line of medical research which has not been very generally investigated. Some of the investigators who have recently contributed to our knowledge in this direction either by suggestions as to method or by the collection of clinical data are Muller,<sup>5</sup> Wohlgemuth,<sup>6</sup> Wynhausen,<sup>7</sup> Boldyreff,<sup>8</sup> Abderhalden and Schittenhelm,<sup>9</sup> Schlecht,<sup>10</sup> Goldschmidt,<sup>11</sup> Volhard,<sup>12</sup> Ury,<sup>13</sup> Frank and Schittenhelm.<sup>14</sup> One of the first enzymes to be

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\*From the Laboratory of Physiological Chemistry of the University of Illinois

1 For previous papers in this series of studies see, I Hawk Univ Penn Med Bull, 1905, xviii, 7, II Fowler and Hawk Jour Exper Med, 1910, vii, 388, III Rulon and Hawk Jour Am Chem Soc, 1910, xxxii, 1686, IV Rulon and Hawk THE ARCHIVES INT MED, 1911, vii, 536, V Hattrem and Hawk THE ARCHIVES INT MED 1911, vii, 610

2 Sahli Deutsch Arch f klin Med, 1898, p 61

3 Schmidt Deutsch med Wchnschr, 1899, No 45

4 Cammidge Proc Roy Soc, London (B), 1909, lxxxi, 372, also Proc Roy Soc Med, iii, 164

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12 Volhard Munchen med Wchnschr, 1908, liv, 403

13 Ury Biochem Ztschr, 1909, xxiii, 153

14 Frank and Schittenhelm Ztschr f exper Path u Therap, 1910, viii,

detected in the feces was pancreatic amylase. This enzyme, as early as 1875, was shown by Wegscheider<sup>15</sup> to be present in the feces of the nursing. This finding was later verified by von Jaksch,<sup>16</sup> Moro<sup>17</sup> and Allaria.<sup>18</sup> According to this last-mentioned investigator the manner of feeding the infant, i. e., naturally or artificially, had no influence on the amylase concentration of the feces. Strasburger<sup>19</sup> found this same condition to hold for the stools of adults.

#### DESCRIPTION OF EXPERIMENTS

Three experiments were made, in each of which normal men (E and W) served as subjects, the same man serving as subject in Experiments 2 and 3. Each experiment was divided into three periods, a *fore* period during which the subject was brought into nitrogen equilibrium through the ingestion of a diet uniform as to quality and quantity from day to day, a *water* period during which the ration was supplemented by the drinking of additional water at meal-time, and finally an *after* period in which the *fore* period ration of low water content was again fed. The constituents of the diet apart from the water were graham crackers, butter, milk and peanut butter. The diet of Subject W in Experiment 1 contained 85.8 gm. of protein per day whereas that of Subject E in Experiments 2 and 3 contained 92.3 gm. of protein per day. During the *fore* and *after* periods of each experiment 100 c.c. of water, in addition to the water content of the milk, was taken by each subject at each meal. In the *water* periods of Experiments 1 and 2, 500 c.c. of water above that previously ingested were taken with each meal, whereas in Experiment 3 this volume was increased to 1½ liters.

Each individual stool was examined in the fresh condition. The feces of one period were separated from those of the next by means of charcoal, the material being ingested in gelatin capsules at the beginning of the first meal of each new period.

The method used in the quantitative determination of the activity of the pancreatic function was that suggested by Wohlgemuth.<sup>20</sup> This author considers that the extent to which pancreatic amylase appears in the feces may be taken as an index of the activity of the pancreatic function. He therefore suggests a procedure for the quantitative determination of the amylolytic power of sodium chloride extracts of the fresh feces. His procedure has been fully discussed by us in another connection and a modification of the Wohlgemuth method proposed.<sup>20</sup> In the experiments

15 Wegscheider Inaug. Diss., Strassburg, 1875

16 Von Jaksch Ztschr. f. physiol. Chem., 1888, xii, 116

17 Moro Jahrb. f. Kinderh., 1898, xlvii, 342

18 Allaria Progresso Med., 1905

19 Strasburger Arch. klin. Med., 1900, lxxvii, 238 and 531

20 Hawk THE ARCHIVES INT. MED., to be published

embraced in the present paper, however, the procedure used by us was essentially that of Wohlgemuth except that the final amylolytic values of the stools were calculated in terms of dry matter instead of on the basis of the moist sediment secured by centrifugation as Wohlgemuth suggests.

In order to demonstrate conclusively the origin of the fecal amylase Wohlgemuth<sup>o</sup> has made certain interesting tests. In these tests it was demonstrated that the ligation of the pancreatic ducts of dogs caused the feces as passed to be amylase-free or to contain at the most a minimal quantity of the enzyme. Wynhausen<sup>21</sup> has likewise found a much-decreased amylase output in cases with partial closure of the pancreatic duct.

TABLE 1—FECAL AMYLASE, EXPERIMENT 1, SUBJECT W, MODERATE WATER DRINKING  
FORE PERIOD—SIX DAYS

Stool No	Feces Fresh (grams)	Dry (grams)	Amylolytic Total (liters)	Value—1% Starch Per Gram Dry Matter (cc)
1	62.8	16.1	11.4	709
2	98.8	26.4	10.8	409
3	109.8	30.2	18.1	600
4	185.8	44.8	26.3	587
5	41.8	13.1	6.7	513
6	104.9	25.5	20.9	819
7	24.0	7.9	3.3	416
Average per day	104.6	27.3	16.3	597

WATER PERIOD—TEN DAYS  
(1,500 cc H<sub>2</sub>O daily)

8	31.6	7.6	7.6	1,000
9	147.5	40.6	34.9	860
10	75.4	19.8	17.1	865
11	144.8	39.8	27.3	688
12	63.9	17.2	14.6	848
13	115.5	31.3	22.2	709
14	26.0	7.2	4.0	548
15	169.0	44.8	32.5	725
16	127.0	30.9	44.7	1,447
17	152.7	35.5	110.3	1,106
Average per day	105.3	27.5	31.5	1,145

AFTER PERIOD

18	60.0	14.8	14.6	983
19	119.6	28.0	29.4	1,052
20	51.1	14.1	20.8	1,477
21	142.7	35.8	41.1	1,147
22	81.4	22.8	15.0	657
23	53.4	16.4	19.1	1,162
Average per day	101.6	26.3	28.0	1,065

#### DISCUSSION OF RESULTS

1 *Moderate Water-Drinking*—Data from the first experiment may be found in Table 1. The subject of this experiment was W and the purpose was the study of the influence of moderate water-drinking *with meals* on the activity of the pancreatic function. After a fore period of six days on a uniform diet, as already mentioned, the subject was found to be in nitrogen equilibrium as was shown by a nitrogen balance of 0.01 + gm. The average daily output of fresh feces was 104.6 gm, representing a dry matter content of 27.3 gm per day during this period.<sup>22</sup> The total

21 Wynhausen. Berl. klin. Wchnschr., 1909, No. 30.

22 The data for fresh and dry feces were obtained by Dr. H. A. Mattill in connection with another research which has already been reported. See Mattill and Hawk. Proc. Soc. Biol. Chem., 1911.

amylolytic value of the stools per day, expressed in liters of 1 per cent starch solution which this feces would hydrolyze under the conditions of the Wohlgemuth method was 16.3 liters. Placed on the basis of "1 gm of dry feces" we see by an examination of the data that the average daily amylolytic value for this period was represented by 597 cc of 1 per cent starch solution.

Under the influence of the 500 cc of water ingested at each meal for a period of ten days there was a marked increase in the amylolytic power of the feces. For example, the data from the first stool of this period indicate that the amylolytic value was 1,000 cc of 1 per cent starch solution per gram of dry feces. This initial value of the period was far above that for any individual stool of the fore period and nearly double that of the daily average amylolytic value (597 cc) for the entire fore period. If the data from the analysis of the stools which were subsequently dropped during this *water* period are examined it will be seen that the amylolytic values for these stools, with a single exception (No. 11), were above the average value for the fore period. It will furthermore be observed that the average amylolytic value for the water period, i. e., 1,115, was approximately twice as great as the average amylolytic value for the fore period. In other words the drinking of 1,500 cc of water per day, at meal time through a period of ten days, was instrumental in causing a virtual doubling of the amylolytic activity of the fecal matter excreted during that period as compared with the fecal output of the fore period during which minimal amounts of water were daily ingested.

The significance of this finding of an increased amylolytic power is further accentuated when the data from the after period are examined. Notwithstanding the fact that the water ingestion of this period was reduced to the low level of the fore period the stools as dropped were on a much higher amylolytic plane than were those of the fore period. This fact is clearly brought out when it is noted that the corresponding values for the fore and after periods were 597 and 1,065 respectively. We thus see that the stimulation of the factors which brought about the increased amylolytic power of the fecal output of the water period was not transitory in character. In other words the influence of the water was not limited to the time of its ingestion, but the factors leading to an increased fecal amylolytic value were so stimulated by the ingestion of the excess water as to continue their efficiency even after the water ration had been again reduced to that of the fore period. Whether this pronounced increase in amylolytic power observed to accompany and follow the ingestion of additional volumes of water at meal time may be properly interpreted as indicative of an increased activity of the pancreatic function is discussed in a later paragraph.

In the second experiment on the influence of moderate water drinking (Experiment 2) E served as subject. All conditions were the same as those in force in the similar experiment on W with the exception that the uniform diet was varied in a minor manner from that ingested by W. The data obtained from the fecal examinations of this experiment are tabulated in Table 2. In this instance approximate nitrogen equilibrium was secured in seven days, the nitrogen balance showing a plus value of 0.485 gm per day. A ten-day water period then followed during which 500 c c of water were ingested with each meal in addition to the uniform water ingestion of the fore period. The experiment ended with a four-day after period.

TABLE 2—FECAL AMYLASE, EXPERIMENT 2, SUBJECT E, MODERATE WATER DRINKING

FORE PERIOD—SEVEN DAYS				
Stool No	Feces Fresh (grams)	Dry (grams)	Amylolytic Total (liters)	Value—1% Starch Per Gram Dry Matter (c c)
1	88.4	18.1	6.3	343
2	30.2	8.0	3.9	491
3	179.2	41.2	14.0	341
4	193.9	47.8	11.3	237
5	76.3	20.1	3.7	184
6	207.7	47.3	16.3	345
7	124.6	27.8	15.3	548
8	44.0	12.9	2.2	171
Average per day	135.0	32.0	10.4	325
WATER PERIOD—TEN DAYS (1,500 c c H <sub>2</sub> O daily)				
9	76.5	17.5	7.3	418
10	140.9	29.4	31.6	1,075
11	63.8	18.6	2.3	124
12	169.0	41.1	16.1	393
13	247.5	47.5	12.1	255
14	135.3	31.1	6.2	198
15	192.4	37.7	19.7	522
16	79.2	19.5	15.6	301
17	55.9	15.2	9.3	613
18	173.5	43.2	27.5	636
19	51.5	14.4	9.2	642
Average per day	138.6	31.5	15.7	498
AFTER PERIOD—FOUR DAYS				
20	67.3	15.9	14.0	878
21	117.8	30.7	19.9	649
22	147.7	34.3	21.8	637
23	145.9	38.7	25.8	667
24	31.2	9.8	9.4	961
Average per day	127.5	32.3	22.7	703

During the preliminary interval of low water ingestion covered by the fore period the average daily total amylolytic value of the feces was equivalent to 10.4 liters of 1 per cent starch solution. Placed on a *dry-matter basis* we find that the amylolytic value of the feces of this period may be represented by 325 c c of 1 per cent starch solution per gram of dry matter. If we now examine the data for the period during which the extra volume of water was ingested we find that the conditions are similar to those already discussed in connection with the experiment in which W served as subject. In other words, water caused an increase in the amylolytic value of the feces. The average total daily amylolytic

value for the water period was 15.7 as against 10.4 for the fore period whereas the value on the dry matter basis was 498 as compared with a value of 325 for the preliminary interval.

The influence of the moderate water-drinking in causing an increase in the amylolytic power of the feces was much less pronounced with E than with W. This statement is borne out by the observation that there was an increase of nearly 100 per cent in the case of W as against an increase of little more than 50 per cent in the case of E. However, when we examine the data for the after periods of the two experiments in question, we note that the amylolytic value in E's experiment was above that of the water period, whereas in W's experiment this value was slightly lower than that of the water period. By calculation we see that the amylolytic value for the after period of the test on W was increased only 80 per cent above that of the fore period whereas the increase in the test on E was about 120 per cent. It would seem, therefore, that the water caused a more pronounced immediate stimulation in the case of W than in that of E but that the influence of the stimulation was more persistent in the case of E than in that of W.

TABLE 3—FECAL ANALYSIS, EXPERIMENT 3, SUBJECT E, COPIOUS WATER DRINKING

FORE PERIOD—SIX DAYS				
Stool No.	Feces Fresh (grams)	Dry (grams)	Amylolytic Value—Total (liters)	1% Starch Per Gram Dry Matter (c.c.)
1	35.2	10.2	3.8	375
2	66.0	18.8	8.6	158
3	202.2	49.8	23.6	473
4	129.2	32.2	14.9	164
5	161.3	31.6	8.8	256
6	171.8	38.8	15.8	406
7	31.6	9.1	1.2	448
Average per day	133.4	32.3	13.3	112
WATER PERIOD—FIVE DAYS (1,000 c.c. H <sub>2</sub> O daily)				
8	90.3	18.2	10.5	578
9	37.2	10.2	8.3	816
10	219.4	58.8	26.5	451
11	74.7	19.9	6.1	306
12	258.0	38.2	34.2	8,961
13	52.6	15.9	7.8	491
Average per day	152.5	32.2	80.3	2,494
AFTER PERIOD—THREE DAYS				
14	128.3	29.6	12.3	414
15	86.1	21.0	15.6	743
16	206.5	44.5	25.0	561
17	50.6	5.6	7.0	1,257
Average per day	157.3	33.6	20.0	595

2 *Copious Water-Drinking*—The amylolytic power of the feces was studied in but one experiment in which copious water drinking was practiced at meal time. In this experiment (3) E served as subject. All the experimental conditions were similar to those in force with this same subject in the second experiment on moderate water drinking. In a fore period covering an interval of six days a very satisfactory balance for income and outgo of nitrogen was obtained, the data indicating a plus balance of only 0.03 gm. The data from this experiment are given in Table 3. An examination of that table will show, in the first place, that

the average total daily amylolytic value for the fore period was 13.3, whereas the amylolytic value on a dry matter basis was 412. These values simply mean, as heretofore explained, that the average output of feces per day during the six-day fore period possessed the power to hydrolyze 13.3 liters of 1 per cent starch solution, whereas 1 gm of dry feces possessed the power of transforming 412 c c of such a starch solution.

The water period of this experiment was five days in duration as against the ten-day periods utilized in the experiments already discussed. However, the daily ingestion of water was much higher in this instance than in either of the afore mentioned studies. In the *moderate* water-drinking tests we caused the subjects to ingest 500 c c additional at each meal or a total daily ingestion of 1,500 c c in excess of that customarily taken. In certain other water-drinking studies made by us (Fowler and Hawk<sup>1</sup>, Mattill and Hawk<sup>22</sup>, also Wills and Hawk, unpublished), in which the influence of *copious* amounts of water was under investigation, the total volume of water added daily to the normal ration had been 3,000 c c. However, in the present investigation we were dealing with a subject, E, who was accustomed to drinking rather larger volumes of water than individuals ordinarily ingest and for this reason his water ration was fixed at 4,000 c c per day during the water period in an attempt to place the daily volume at such a figure as should be copious for his organism. He felt no personal discomfort at any time during the period in which this excessive amount of water was being daily introduced into his system.

Under the influence of copious water-drinking through a five-day period, the amylolytic activity of E's feces was increased in an extremely emphatic manner. Particularly was this true of Stool 12, passed on the fourth day of the period. Expressing the amylolytic values in the same manner as heretofore followed we find that the average amylolytic power of the feces was equivalent to a force sufficient to hydrolyze 80.3 liters of 1 per cent starch solution. Furthermore, if we transfer the comparison to the dry-matter basis we learn that 1 gram of dry matter represents sufficient amylolytic activity to hydrolyze 2,494 c c of 1 per cent starch solution. When we compare these volumes with those obtained during the fore period we are astounded at the very material increase in the amylolytic activity which has taken place under the influence of the copious water-drinking. For example, if we consider the dry-matter basis we see that the amylolytic value has increased from 412 to 2,494, a most surprising increase of more than 600 per cent in the amylolytic activity. The question as to the proper interpretation of this finding, in so far as it relates to the functional activity of the pancreas, is discussed later on. In this experiment for the first time, we observed an amylolytic value for the after period which was lower than that of the water period. Evi-



dently the stimulation of the copious water-drinking was so pronounced in character in this particular instance as to rather militate against any further added stimulation after the organism was released from the immediate influence of the water ingestion. That the influence of the water extended somewhat beyond the time interval during which it was actually being ingested is gathered from the recorded average amylolytic values for the after period. These values are nearly 45 per cent above those of the fore period thus indicating an after effect which persisted for a time, at least, after the period of high water intake had closed.

#### INTERPRETATION OF FINDINGS

The foregoing discussion of the various experiments embraced in this study has indicated clearly that when either small or large volumes of water above those customarily ingested were taken at meal time that the resultant fecal matter possessed greater amylolytic activity than did the feces passed during periods in which these extra volumes of water were not taken. How is this finding to be interpreted? It has been established that an increase in the activity of the pancreatic function will be indicated by the appearance of an added excretion of pancreatic amylase in the feces. This fact would of itself cause the feces in question to possess an increased power to hydrolyse starch solution. On such a basis Wohlgemuth has suggested a method for the quantitative determination of the amylolytic power of the feces. This power, according to Wohlgemuth, is due entirely to the ability of dilute solutions of the fecal amylase to transform starch into substances which no longer give a blue color with iodine. From this point of view, therefore, we may interpret our results as indicating that the pancreatic function has been greatly stimulated under the influence of the water-drinking at meal-time and that consequently larger quantities of pancreatic amylase are present in the feces passed during the water period, thus giving to the fecal matter a higher amylolytic power than that possessed by stools dropped during previous periods in which the water ingestion was minimal.

We began our investigation under the impression that Wohlgemuth's method would furnish us with accurate data, and nothing occurred in the course of the experiments to cast any doubt on the validity of Wohlgemuth's claim until an examination was made of the final stool (17) in the water period of Experiment 1. Here for the first time in the course of our studies the entire series of seven tubes of 1 per cent starch solution showed complete digestion. As soon as this fact was determined another series of ten tubes was prepared and again the entire series was completely digested. Not caring to rely on data obtained from further extracts because of the possibility of changes having taken place in the feces, we examined no further series. A similar observation was made in

connection with Stool 12 in Experiment 3. In our search as to the cause of this surprisingly pronounced increase in the amylolytic activity of the stools mentioned, we observed that they each possessed a very pronounced acid reaction. We were familiar with the findings of Chittenden and Griswold,<sup>23</sup> which were later confirmed by Vernon<sup>24</sup> to the effect that amylase (salivary) is inactive in the presence of 0.009 per cent hydrochloric acid. At the same time we were familiar with the further fact that it requires an acid concentration much above 0.009 per cent hydrochloric acid to hydrolyze 1 per cent starch solutions under the conditions of our experiment. Furthermore, in the experiments of Vernon to which reference has already been made, as well as in others by Schierbeck,<sup>25</sup> it has been demonstrated that certain proper acid concentrations below 0.009 per cent hydrochloric acid will facilitate the activity of amylase. This power was shown to be possessed by organic acids as well as by inorganic acids. In the case of hydrochloric acid a concentration of 0.004 per cent was found to cause an increase of 400 per cent in the amylolytic power of the enzyme, whereas 0.0083 per cent lactic acid increased the amylolysis nearly 500 per cent.

In light of the above findings, we might interpret the fivefold increase in the amylolytic power of acid Stool 17 of Experiment 1 and the sixfold increase in the amylolytic power of acid Stool 12 of Experiment 3 as due to the stimulating influence of the acid reaction of the sodium chloride extracts of the feces on the contained amylase. It obviously needs no argument to support the claim that the acidity of these extracts could not of itself have caused the hydrolysis of the 1 per cent starch solutions. Even had the feces possessed a surprisingly high acid concentration, this concentration must of necessity have been so much lowered by the time the series of dilutions of the salt solution extracts had been made as to render the acidities, of the latter part of the series, at least, of no influence in so far as their power to hydrolyze starch is concerned. It is entirely possible that the amylase was passed into the intestine in increased amount on the days in question under the influence of the high water intake, that it there fulfilled its function of bringing about an augmented amylolysis and that subsequently the reaction of the surrounding media was so altered by certain factors as to render impossible any further activity of the enzyme. Therefore the reaction in which the enzyme was finally excreted from the organism by way of the feces was not, of necessity, the reaction which the intestinal substrate of the pancreatic amylase possessed. Be that as it may, however, it is of course impossible to come to any definite conclusion as to the extent of the stimulation of the activity of the pancreatic function on the basis of data collected from acid

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23 Chittenden and Griswold. *Am. Chem. Jour.*, 1881, *111*, 305.

24 Vernon. *Jour. Physiol.*, 1902, *xxvii*, 174.

25 Schierbeck. *Skand. Arch. f. Physiol.*, 1892, *111*, 344.

stools by means of the Wohlgemuth method. This being so, we have suggested a modification of that method which should obviate the troublesome features associated with the examination of stools which possess a pronounced acid or alkaline reaction. This method appears elsewhere<sup>26</sup>

If we examine the data in Tables 1, 2 and 3 it will be seen that the complete elimination of all consideration of the acid stools in question which gave evidence of the surprisingly pronounced amylolytic power, will not prevent us from drawing the conclusion that the activity of the pancreatic function was stimulated under the influence of water-drinking at meal time. Certain other experiments may be cited as tending to substantiate the theory of an increased activity of the pancreatic function under the influence of water-drinking with meals. For example, Pawlow<sup>26</sup> has shown that if 150 cc of water be introduced into the stomach of a dog possessing a pancreatic fistula, that the flow of juice begins after an interval of two or three minutes and in case there is already present a distinct flow of juice that the output is distinctly increased. That this flow of juice was not brought about through the stimulation of acid chyme entering the duodenum was shown from the fact that, if the stomach of the animal be emptied, the contents of the organ are found to be neutral or faintly alkaline in reaction. This experiment by Pawlow indicates clearly, then, that water introduced into the stomach causes a direct stimulation of the nervous mechanism of the pancreas which is followed by an outpouring of pancreatic juice. As further basis for our belief that water ingestion stimulates the pancreas, we would cite certain other experiments of Pawlow<sup>27</sup> and the earlier work of Heidenhain<sup>28</sup> and Ssanowski<sup>28</sup>. The more recent experiments of Foster and Lambert<sup>29</sup> may also be adduced as furthering this claim. These various investigators just enumerated have shown that an increased flow of gastric juice follows the entrance of water into the stomach. The studies of Foster and Lambert go even farther than this and show most clearly that there is not only an increased flow of juice but that this increased volume possesses a higher acid concentration than that possessed by juice secreted under other conditions. We have obtained results in this laboratory<sup>30</sup> which go to verify the findings of Foster and Lambert. On the basis of the well-established theory as to the mechanism of pancreatic secretion as evolved by Bayliss and Starling<sup>31</sup> we may logically expect a pronounced increase in the flow of pancreatic juice to follow the entrance of the strongly acid chyme into the duodenum. That the pancreas is more active under a

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26 Pawlow. *The Work of the Digestive Glands*, Second Edition, 1910, p. 144

27 Pawlow. *The Work of the Digestive Glands*, p. 112

28 Quoted by Pawlow, p. 112

29 Foster and Lambert. *Jour. Exper. Med.*, 1908, x, 820

30 Wills and Hawk. *Proc. Soc. of Biol. Chem.*, 1911

31 Bayliss and Starling. *Jour. Physiol.*, 1902, 28

high water ingestion is also evidenced from other experiments made in this laboratory<sup>22</sup> which have demonstrated a more complete digestion and absorption of ingested fats and carbohydrates under the influence of water-drinking at meal time

It has further been found by us<sup>32</sup> that the carbohydrate content of the actual samples of feces listed in Tables 1, 2 and 3 of this article was lower during the water periods than during the period of minimal water ingestion. This fact demonstrated definitely then that the intestinal content of these subjects was of a higher amylase concentration during the period of increased water intake. Other things being equal we would expect a fair degree of uniformity between the availability of ingested carbohydrate and the content of fecal amylase. The observation of Bradley<sup>33</sup> to the effect that pancreatic lipase possesses greater fat-splitting power when its reaction mixtures are diluted with several volumes of water also goes far toward a substantiation of the theory of a pancreas activated through water ingestion.

We have much to learn as to the alterations in the reaction of the intestine under different conditions. In the case in point we have an excessive quantity of hydrochloric acid passed into the intestine, under the influence of the high water intake, a quantity which probably, at times, is far in excess of that which may be neutralized by the pancreatic juice and bile. The greater portion of this excess acid we may suppose to be neutralized by the ammonia which is produced in the deamidation of protein material. This acid would therefore appear in the urine as ammonium chlorid. However, if there should occur a very copious outpouring of hydrochloric acid at a time when there was but little protein material available for deamidation and consequently a minimal amount of ammonia present for the neutralization of such excess acid, it is entirely possible that we might have an acid reaction due to hydrochloric acid extending the entire length of the large intestine. In that event the stools would probably possess a relatively high acid concentration. If the food residues remained in the intestine for an interval shorter than the normal because of increased peristalsis, diarrhea, etc., acid stools might also result.

The normal reaction of the intestinal contents is acid down to the ileocecal valve under normal conditions. Furthermore, carbohydrates which escape absorption may undergo acid fermentation through the action of certain acid-forming bacteria such, for example, as *Bacillus coli* and *Bacterium welchii*. A number of organic acids are formed which include acetic acid, lactic acid, butyric acid and succinic acid. The extent to which this acid reaction may be carried is indicated by Macfadyen,

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32 Mattill and Hawk. Unpublished results.

33 Bradley. Journal Biol Chem, 1910, viii, 251.

Nencki and Sieber's<sup>34</sup> finding of an acidity at the ileocecal valve equivalent to 0.1 per cent acetic acid. This observation was made on a patient with a fistula at the end of the small intestine.

#### SUMMARY

The problem studied was the activity of the pancreatic function under the influence of water-drinking at meal time. Normal men were used as subjects and were required to ingest a diet uniform in all respects from day to day. Three experiments were made, each experiment being divided into three periods, a *fore* period in which the subject was brought into nitrogen equilibrium through the ingestion of the uniform diet supplemented by a minimal water ingestion, a *water* period during which the water ingestion at meal time was increased from 1,500 to 4,000 c.c. per day, and an *after* period in which the dietary conditions of the *fore* period prevailed. Two of the experiments were on the influence of *moderate* water-drinking and in these the volume of the extra water ingested during the *water* period was 1,500 c.c. per day or 500 c.c. per meal. In the third experiment the influence of *copious* water-drinking was studied and in this instance the subject was required to ingest on each day of the *water* period 4,000 c.c. above that ingested in the *fore* and *after* periods.

The amylolytic activity of the feces, denoting, according to Wohlgemuth, the content of pancreatic amylase present in the feces, was taken as the index of the activity of the pancreatic function. The amylolytic values for the stools dropped during the periods of moderate and copious water-drinking at meal-time were much higher than the similar values as determined for the stools dropped during the periods of minimal water ingestion. This finding may be interpreted as indicating that the drinking of water with meals had stimulated the pancreas. We make this interpretation with certain reservations regarding conditions not controlled by the Wohlgemuth method. Two stools were encountered in the course of the investigation which exhibited a pronounced acid reaction. Inasmuch as the basic principle of Wohlgemuth's method is the hydrolysis of starch solutions through the medium of unneutralized fecal extracts, the method does not give dependable data as to the amylase content when such stools are under examination. This is true especially in view of the fact that it has been shown that 0.004 per cent hydrochloric acid will increase the activity of amylase 400 per cent, whereas 0.009 per cent hydrochloric acid will cause absolute inhibition. The power of feces extracts, therefore, to hydrolyze starch cannot be taken as a measure of the amylase present unless precautions are taken to neutralize the fecal extracts and then make the conditions uniform for the action of the enzyme if present.

<sup>34</sup> Macfadyen, Nencki and Sieber. Arch. f. exper. Pathol. u. Pharmacol., 1891, xxviii, 311.

On the basis of the data gathered in this and in associated investigations made in our laboratory and elsewhere, we are prepared to draw the general conclusion that the ingestion of quantities of water at meal-time ranging in volume from  $\frac{1}{2}$  to  $1\frac{1}{3}$  liter stimulate the pancreatic function in two ways first, a direct stimulation of the nervous mechanism of the pancreas brought about while the water is still in the stomach and, second, an indirect stimulation brought about on the entrance of the increased volume of acid chyme into the duodenum. The drinking of water with meals ought therefore to bring about a more rapid and complete digestion and absorption of the fat and carbohydrate constituents of the diet, two observations verified by experimentation in our laboratory.

# THE IMMEDIATE EFFECT ON THE COMPLEMENT FIXATION TEST FOR LUES OF TREATMENT WITH SALVARSAN (ARSENOBENZOL)

AN ANALYSIS OF 225 CASES\*

CHARLES F. CRAIG, M.D.†

WASHINGTON, D. C.

In reviewing the literature on the results of the treatment of lues with salvarsan, one is impressed with the unsatisfactory nature of the data regarding the effect of treatment with this drug on the complement fixation test. It is now generally acknowledged that this test is the only exact index we possess of the efficacy of any method of treatment of lues, indeed, Ehrlich<sup>1</sup> does not hesitate to say that "the observation of the Wassermann reaction represents the most valuable method we have of seeing clearly whether the syphilis is genuinely cured," and this opinion is supported by every authority having to do with the treatment of the disease.

In view of the importance of the complement fixation test as a control of the efficacy of treatment with salvarsan, I have thought that an analysis of 225 cases, showing the immediate effect of such treatment on the test, would be of interest and value. I have used the term "immediate effect" because it is yet too early to speak of the ultimate effect of this method of treatment on the complement fixation test. It is believed that the data obtained from the cases reported on are especially valuable, because in the vast majority numerous tests have been made at frequent intervals, thus giving one a more just conception of the exact effect of treatment with this drug on the complement fixation test. It will be observed that an early disappearance of a positive reaction is more frequently noted in this series of cases than is reported by most observers, largely owing to the fact that the tests were made at frequent intervals a practice possible only in the military service or where luetic patients can be kept under constant observation for long periods of time. In the military service, also, it is possible to secure more accurate data regarding the date of infection and the nature and extent of previous treatment,

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\*From the Bacteriologic Laboratory of the Army Medical School, Washington, D. C.

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‡Captain, Medical Corps, U. S. Army.

<sup>1</sup> Ehrlich, P. *Chemotherapy*, Ed. 1, New York, 1911, p. 116.

facts of great importance in any consideration of the effect of treatment with salvarsan on the complement fixation test

Before considering the results obtained in this laboratory, it is necessary briefly to discuss the exact clinical significance of the positive and negative reaction after treatment with salvarsan. I believe that it may be stated without hesitation that a positive Wassermann reaction means the presence of living spirochetes and is always an indication for further treatment, provided a sufficient time has elapsed for the reaction to become negative, as shown by experience. On the other hand a negative reaction does not necessarily mean that all the spirochetes are destroyed, for relapses may occur after the reaction has been negative for weeks or even months. A negative reaction may, therefore, mean either a complete cure or only the destruction of a sufficient number of the spirochetes to prevent the appearance of the reaction. The latter statement is supported by the occurrence of cases in which the patients are suffering from a clinical relapse, but in which the complement fixation test remains negative for some time. In one such case the spirochetes were demonstrated in the lesions at the time of the relapse, although the reaction was still negative, thus proving that the mere presence of the parasites is not always accompanied by a positive Wassermann test. Well-marked clinical cases of lues are also observed, in which the Wassermann test is negative, although the lesions contain the spirochetes and no treatment has been administered. It would, therefore, appear as though the appearance of a positive reaction depends on quantitative phenomena or on reactions of the tissues to the spirochetes which may not occur under certain conditions.

As I have stated the literature regarding the effect of treatment with salvarsan on the complement fixation test is limited in amount, and much of it is unsatisfactory in character. While many authorities have reported very fully the clinical results in thousands of patients so treated the serologic data are generally incomplete, many of the most valuable clinical reports containing either no mention of the results of the complement fixation test or recording them inaccurately or in such a way that no definite conclusions can be drawn from them. A few writers, however, have reported in detail the results of the Wassermann test in their cases but it is difficult to judge of their value, as a whole, on account of the lack of data regarding many important factors having to do with the time of disappearance of the reaction. A brief abstract is given of the most important contributions to this subject.

Nichols and Fordyce<sup>2</sup> report the results of the Wassermann test in eleven patients treated with salvarsan. In eight the reaction became negative, one in nineteen days, two in twenty one days, one in twenty-three days, one in twenty-five days, one in thirty-nine days, one in three months, and one in three months

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2 Nichols, H J, and Fordyce, J A. Jour Am Med Assn, 1910, lv, 1171



and eleven days. Of these cases, two are still negative at the end of ten months, a period of time sufficient, I believe, to prove that they are cured. In both of these cases, the dose of arsenobenzol was only 0.3 gm. Relapses occurred in two cases and the remainder have disappeared.

Gerronne and Huggenberg<sup>3</sup> report ten cases in which a plus reaction became negative in from four to ten weeks. In four cases it remained positive, one after fifty-six days, and one after seventy days. In twenty-five cases observed for less than four weeks only six became negative.

Michaelis<sup>4</sup> treated 110 patients and observed only three relapses. He states that the serum reaction may become negative within a period from two to ten weeks after the injection. He observed in some instances a strengthening of the reaction after treatment, although the clinical symptoms were disappearing.

Fordyce<sup>5</sup> states that the results of the Wassermann test after "606" have varied within wide limits but in general a change occurred in from four to five weeks. The earliest change from a positive to a negative reaction observed by him was in six days after the injection, but in another case, after two injections, the reaction did not become negative until fifty-two days. Another case, after two injections, was still positive after seventy-one days and another after 102 days. He says that "several cases showed alternating negative and positive phases."

Hersheimer<sup>6</sup> records the results of 789 treated cases of which thirty-three relapsed in a period of five months. Many of his patients disappeared before a negative reaction was obtained. He observed a negative reaction in two primary cases after seven and twenty days, while four cases which were negative before the treatment became positive afterwards. Of thirty secondary cases that became negative after treatment, five became negative in from one to two weeks, the others at later periods. In seven latent cases, three became negative in from eight to fourteen days.

Wenstraud<sup>7</sup> reports that in only thirty-seven out of seventy-seven patients, did the Wassermann reaction become permanently negative, and that in three cases it remained positive after three injections of arsenobenzol.

TABLE 1—RESULTS OF COMPLEMENT FIXATION TEST AFTER TREATMENT WITH SALVARSAN (FAVENTO)

Stage of Disease	Remained Positive	Became Negative	—Time of Disappearance of Reaction in Weeks—							
			1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
Primary	0	15	1	4	2	3	4	0	0	1
Secondary	12	16	1	4	2	3	3	3	0	0
Tertiary	4	1	0	0	1	0	0	0	0	0
Totals	16	32	2	8	5	6	7	3	0	1

Favento<sup>8</sup> records very carefully the serologic data in forty-eight cases of lues in which salvarsan was used, Table 1 giving his results.

It will be observed that the majority of his cases became negative in from two to five weeks after the injection. Some of his positive cases were only observed for three or four weeks and, therefore, may have become negative later.

3 Gerronne and Huggenberg. Berl klin Wehnschr, 1910, xlvii, 28

4 Michaelis, L. Berl klin Wehnschr, 1910, xlvii, 1195

5 Fordyce, J. A. New York Med Jour, 1911, xcii, 897

6 Hersheimer, G. Deutsch med Wehnschr, 1910, xxvii, 1517

7 Wenstraud, C. Med Klin, 1910, xliii, 183

8 Favento, A. Munchen med Wehnschr, 1910, lvii, 2080

Noguchi<sup>9</sup> has recently published a very valuable serological analysis of 102 cases, in which the patients were treated with salvarsan. He states that more than half of the number were under observation for over three months, while the remainder had been injected for four weeks. He conducted a quantitative determination of the serum reaction in each case, the blood being examined before the injection and at intervals of one day, three days, one week, two weeks, three weeks, four weeks, six weeks, eight weeks, etc., after the injection. He found that thirty cases became negative, twenty-four reduced to less than 1 antibody unit, while the remaining forty-eight cases still contain more than 1 antibody unit, giving strong positive reactions. However, a titration of the serum of these cases showed that they were decidedly reduced in antibody content, although they gave strong reactions. In 40 per cent of the primary cases, in 37 per cent of secondary, in 35 per cent of tertiary, in 33 per cent of latent, in 14 per cent of hereditary, and in 50 per cent of incipient tabes, the reaction became negative. The average of the negative reactions equaled 33.7 per cent of the total 102 cases. Ten relapses were observed, six of the patients were reinjected with good results and one had a second relapse. Of the negative cases reported by Noguchi, thirty-four in number, three became negative in two weeks, ten in three weeks, eleven in four weeks, five in five weeks, four in six weeks, and one in seven weeks. His results in this respect are similar to those obtained in this laboratory.

It will be noted that there is the greatest variation in the results obtained by different observers, and the number of cases which have been reported serologically is very small when compared with the vast number in which salvarsan treatment has been used. The difference in results may be explained by the class of patients treated by different observers, the amount and kind of previous mercurial treatment, and, perhaps, by the technic employed in making the tests.

#### THE DISAPPEARANCE OF THE REACTION IN RABBITS INFECTED WITH LUES AND YAWS

Through the kindness of Captain Nichols of the Army Medical Corps, I have recently had the opportunity of testing rabbits experimentally infected with lues and yaws, and of observing the complement fixation curve as shown by the titration of the serum of these animals, as regards its complement fixation qualities. Table 2 illustrates the results obtained in an animal infected with lues and Table 3 in one infected with yaws, these will show the gradual increase in the anti-body strength of the serum and the disappearance of the positive reaction after the administration of salvarsan.

An examination by Captain Nichols of Rabbit 39, infected with lues, demonstrated the presence of spirochetes on January 19, but the Wassermann test was not positive, even with 0.2 c.c. of serum, until January 23. From this time it gradually increased in strength until February 6, at which time 0.05 c.c. of the serum gave a double-plus reaction. At this time Captain Nichols administered intravenously 0.02 gm. of salvarsan per kilo and the reaction became negative on January 13, one week

<sup>9</sup> Noguchi, H. Serum Diagnosis of Syphilis, Ed. 2, Philadelphia, 1911

after treatment. It is interesting to observe that the reaction diminished in strength on the 8th and increased in strength on February 10, after treatment.

In Rabbit 11, infected with yaws, the spirochetes were demonstrated by Captain Nichols on January 21, but the Wassermann test did not become positive until January 30. On February 6, when 0.05 cc of the serum gave a double-plus reaction, 0.02 gm of salvarsan per kilo was administered intravenously by Captain Nichols, and on February 13 the reaction became negative, one week after treatment. Here again it is interesting to observe a diminution in the strength of the reaction two days after treatment, an increase four days after treatment, and a final disappearance three days later. Similar phenomena have been noticed in human subjects, a negative reaction becoming positive after treatment or weak reactions becoming strong for a short period after the administration of salvarsan. Ehrlich believes that such changes in the reaction are due to the reaction of the tissues to poisons liberated by the destruction of the spirochetes.

TABLE 2—RESULTS OF COMPLEMENT FIXATION TEST BEFORE AND AFTER TREATMENT WITH SALVARSAN IN RABBIT 39, INFECTED WITH LULS\*

Amount of Serum	Date of Tests							
	1/23	1/27	1/30	2/6	2/8	2/10	2/13	2/18
0.05 cc	—	+	+	++	—	+	0	—
0.10 cc	—	++	++	++	±	++	—	—
0.15 cc	0	++	++	++	±	++	0	—
0.20 cc	++	0	++	++	±	++	—	—

\* Spirochetes found in testicular lesion Jan. 19, 1911, 0.02 gm salvarsan per kilo administered intravenously Feb. 6, 1911.

TABLE 3—RESULTS OF COMPLEMENT FIXATION TESTS BEFORE AND AFTER TREATMENT WITH SALVARSAN IN RABBIT 41, INFECTED WITH YAWS\*

Amount of Serum	Date of Tests							
	1/23	1/30	2/2	2/6	2/8	2/10	2/13	2/17
0.05 cc	—	—	++	++	—	—	—	—
0.10 cc	—	±	++	++	—	±	—	—
0.15 cc	—	+	++	++	+-	+	—	—
0.20 cc	—	++	++	++	+-	++	—	—

\* Spirochetes found in lesion Jan. 21, 1911, 0.02 gm salvarsan per kilo administered intravenously Feb. 6, 1911.

The results in this laboratory of the complement fixation tests in experimentally infected animals before and after treatment with salvarsan have been perfectly consistent throughout and prove indubitably the specific action of this drug on the spirochetes of syphilis and yaws.

#### TECHNIC AND GENERAL RESULTS

The technic used in making the tests in this laboratory is largely that recommended by Noguchi. A human hemolytic system has been used, the amboceptor being obtained from rabbits immunized against human

red corpuscles As antigen we have used an extract of luetic fetal liver in absolute alcohol and the serum tested has always been inactivated As we receive our specimens from army posts, many of them located at considerable distances from the laboratory, we use only inactive serum and for this reason have preferred an alcoholic extract as antigen Guinea-pig serum has been used for complement One cubic centimeter of a 1 per cent suspension of red corpuscles is used for the antigen and control tubes The technic of making the test will not be considered, as it is familiar to all who are interested in the Wassermann reaction

Our tests have been controlled by repeated tests made at the same time on known clinical cases and the results have always been consistent

At the present writing complement fixation tests are being made in this laboratory on over 700 soldiers who have been treated with salvarsan, but I have only considered the results in 225 cases, for the reason that the remainder have not been observed for a sufficient time for the data to be of definite value Of the cases reported on all have been observed for at least eight weeks since the administration of the drug and most of them for a longer period

Of the 225 cases reported 164, or 72.8 per cent, became negative and sixty-one, or 27.1 per cent, have remained positive Of the 164 cases which became negative, twenty-four, or 14.6 per cent, have relapsed, forty-three have remained negative for two months, forty-one for two and one-half months, twenty for three months, seven for four and one-half months, eleven for five and one-half months, seven for six months, and six for seven months It is probable that some of these cases will relapse later, but it is not believed that relapses will occur in a very large proportion of them

A number of important factors must be considered in order to understand the exact value of these data The number of cases which remain positive, or become negative after the administration of salvarsan is of little practical significance unless we are informed as to the stage of the disease in which the drug is administered, the intensity of the positive reaction, the method of administration, and the amount and kind of previous mercurial treatment In view of the importance of these factors, I have endeavored to give a complete analysis of the cases in these respects, and I believe that the real effect of treatment with salvarsan on the complement fixation test can be accurately ascertained only when such an analysis is made In the literature dealing with this subject but little attention seems to have been paid to the factors which I have mentioned, and therefore much of it is comparatively valueless

# THE STAGE OF THE DISEASE IN RELATION TO THE DISAPPEARANCE OF THE REACTION

The results obtained in this laboratory show that the immediate effect of treatment with salvarsan on the complement fixation test is much influenced by the stage of the disease. In Table 4 is given an analysis of the cases reported, showing the number becoming negative and remaining positive in the various stages of lues. The data are based on the results of one injection of salvarsan in all but a few cases, the dose employed varying from 0.5 to 0.8 gm.

TABLE 4.—THE RESULT OF TREATMENT WITH SALVARSAN ON COMPLEMENT FIXATION IN THE VARIOUS STAGES OF LUES

Stage of Disease	No. of Cases	Became Negative	Per Cent	Remained Positive	Per Cent	Relapsed	Per Cent
Primary	31	25	80.6	6	19.4	3	12
Secondary	135	100	74	35	25.9	15	15
Tertiary	22	12	54.9	10	45	2	16.6
Latent	37	27	72.9	10	27	4	14.8
Totals	225	164	72.8	61	27	24	14.8

It will be observed from a consideration of the table that of thirty-one primary cases 80.6 per cent became negative, while 12 per cent relapsed. In the secondary cases 135 in number, 74 per cent, became negative, of which 15 per cent relapsed. In the tertiary cases twenty-two in number, 54.9 per cent, became negative, of which 16.6 per cent relapsed, and in the latent cases thirty-seven in number, 72.9 per cent became negative and 14.8 per cent relapsed. It is thus evident that the best results were obtained, as regards the disappearance of the reaction, in the treatment of patients in the primary stage and the most unfavorable in the treatment of patients in the tertiary stage. In latent cases the results are apparently somewhat better than in the secondary cases, and it is interesting to note the gradual decrease in the efficacy of the treatment the older the active stage of the disease. The results obtained are as might be expected and indicate the value of early treatment of luetic infections.

The time of disappearance of the reaction in the cases which became negative has also varied with the stage of the disease. In Table 5 is given the date of disappearance of the reaction in weekly periods correlated with the stage of the infection.

It will be noted that, considering the total number of cases, the greatest number became negative during the second, third and fourth weeks, that a considerable number became negative one week after injection, and that, in our experience, none of the cases became negative after eight weeks. I believe that unless the reaction becomes negative within this time it will not become so later, in the vast majority of cases, and

that a positive reaction after this period should always be considered an indication for further treatment

In regard to the time of disappearance of the reaction in relation to the stage of the disease, it will be noted that the best results were obtained in the tertiary stage, no less than nine of the twelve tertiary cases becoming negative within two weeks, and that four weeks was the longest time after treatment in which the reaction became negative at this stage of the disease. In the secondary cases the reaction disappeared most frequently during the second, third and fourth weeks, while the longest period was eight weeks. In the primary cases thirteen of the twenty-five cases became negative within two weeks, while five weeks was the longest period after treatment that the reaction became negative. In latent cases the majority became negative during the second, third, fourth and fifth weeks, and no case became negative after six weeks.

TABLE 5—THE RELATION OF THE STAGE OF LUES TO THE TIME OF DISAPPEARANCE OF COMPLEMENT FIXATION, AFTER TREATMENT WITH SALVARSAN

Stage of Disease	No of Cases	Time of Disappearance of Reaction							
		1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
Primary	25	2	11	7	4	1	0	0	0
Secondary	100	10	24	24	17	10	10	4	1
Tertiary	12	3	6	2	1	0	0	0	0
Latent	27	2	6	4	5	6	4	0	0
Totals	164	17	47	37	27	17	14	4	1

The favorable results obtained in the tertiary cases, as regards the disappearance of the reaction, coincide with the remarkable influence of salvarsan on the lesions of this stage of the disease, as described by many clinicians, and they would appear to indicate that unless the reaction becomes negative within a month the majority of the patients require further treatment. In considering our results in this stage of the disease, it should be remembered that almost all of the patients had received more or less vigorous mercurial treatment, which undoubtedly had weakened the infection and thus led to an early disappearance of the reaction after the administration of salvarsan. In fact, in the majority of our cases of secondary, tertiary and latent lues mercurial treatment had been administered and the effect of this on the disappearance of the reaction will be considered later.

#### THE RELATION OF THE INTENSITY OF COMPLEMENT FIXATION TO THE DISAPPEARANCE OF THE REACTION

From the study of the intensity of the reaction in the cases here reported on, it is apparent that the stronger the reaction the smaller the number of cases which become negative. In the tables given in this

paper a double-plus reaction indicates complete inhibition of hemolysis a plus reaction at least 50 per cent of inhibition, and a plus-minus reaction less than 50 per cent of inhibition. Classified in this way the relation of the intensity of the reaction to the time of disappearance is illustrated in Table 6.

TABLE 6—THE RELATION OF THE INTENSITY OF COMPLEMENT FIXATION TO THE RESULTS OF TREATMENT WITH SALIVARSAN

Character of Reaction	No. of Cases	Became Negative	Per Cent	Remained Positive	Per Cent	Relapsed	Per Cent
++	119	79	66.3	40	33.6	13	16.4
+	71	57	80.2	14	19.7	7	12.2
±	35	28	80	7	20	1	14.2
Totals	225	164	72.8	61	27.1	21	11.6

An analysis of this table shows that of 119 cases in which the reaction was double-plus 66.3 per cent became negative, of which number 16.4 per cent relapsed. Of seventy-one cases in which the reaction was plus 80.2 per cent became negative, of which 12.2 per cent relapsed. Of thirty-five cases in which the reaction was plus-minus 80 per cent became negative and 14.2 per cent relapsed. It will be observed that in the double-plus cases a smaller percentage became negative and a larger percentage relapsed than in either the plus or plus-minus cases and it would, therefore, appear that the conclusion is justified that the prognosis, as regards the disappearance of the reaction, is less favorable in cases giving a double-plus reaction. Of course, this is to be expected if the intensity of the complement fixation test is a measure of the severity of a luetic infection, but it is more difficult to explain why the percentage of disappearances is less and of relapses greater in the plus-minus cases than in those giving a plus reaction, as shown in the table, although a careful inquiry into the history of our cases indicates why this is so. Nearly half of the cases giving a plus-minus reaction were patients in the late secondary or tertiary stages of the disease in which the infection was still active, although they had been treated vigorously with mercury and the weak reaction in these cases is explained by the fact that mercurial treatment was omitted only a short time before the serum was tested. Had all of our plus-minus cases been in the primary or early secondary stage of the disease I believe that the percentage of disappearance would have been higher than is indicated in the table, while the relapses would have been fewer in number. The relation which the intensity of complement fixation bore to the actual time of disappearance of the reaction in the 164 cases which became negative is shown in Table 7.

This table shows that most of the cases giving a double-plus reaction became negative during the second, third and fourth weeks after treatment, the greatest number during the second week, but that no less than eight became negative during the first week after treatment. The results were similar in the cases giving a plus reaction, although a smaller number, proportionately, became negative in the first week. As would be expected the cases giving a plus-minus reaction showed the largest proportion becoming negative in the first week but some did not become so until the fifth and sixth week. The quickest results were obtained in the plus-minus cases, considered as a whole, while the results in the double-plus and plus cases were practically the same.

TABLE 7—THE RELATION OF THE INTENSITY OF COMPLEMENT FIXATION TO THE TIME OF DISAPPEARANCE OF THE REACTION AFTER TREATMENT WITH SALVARSAN

Character of Reaction	No of Cases	Time of Disappearance of Reaction							
		1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
++	79	8	22	18	13	8	6	4	0
+	57	2	16	14	11	6	7	0	1
±	28	7	9	5	3	3	1	0	0
Totals	164	17	47	37	27	17	14	4	1

The early disappearance of the reaction in the double-plus cases was largely due to the fact that many of these were primary and secondary cases, some of which had received previous mercurial treatment and the amount and kind of such treatment must always be considered in interpreting the real meaning of early disappearances of the reaction.

The relation of the stage of the disease and the intensity of the reaction to the time of its disappearance after treatment with salvarsan is shown in Table 8.

In analyzing this table it is necessary to consider the intensity of the reaction in relation to its disappearance in each stage of the disease. Of the twelve primary cases giving a double-plus reaction 83.3 per cent became negative, of which 30 per cent relapsed, of the seventy-six secondary cases giving a double-plus reaction 63.1 per cent became negative, of which 18.9 per cent relapsed, of the ten tertiary cases with a double-plus reaction 40 per cent became negative and 50 per cent relapsed, and of the twenty latent cases giving a double-plus reaction 70 per cent became negative, of which 14.2 per cent relapsed.

Considering these cases as a whole it will be observed that the best results, as regards the disappearance of the reaction, were obtained in the primary stage and the poorest in the tertiary stage, while better results were obtained in the secondary stage than in latent infections. When



relapses are considered, however, the best results were obtained in the latent cases and the poorest in the tertiary cases, the secondary stage gave better results as regards relapses than the primary and this was not due, as might be thought, to either the method of the administration of the drug or to the dosage

TABLE 8—RELATION OF THE STAGE OF LUIS AND THE INTENSITY OF THE COMPLEMENT FIXATION REACTION TO ITS DISAPPEARANCE AFTER TREATMENT WITH SALVARSAN

Stage of Disease and No of Cases	Character of Reaction	Became Negative	Per Cent	Remained Positive	Per Cent	Relapsed	Per Cent
Primary	++	10	83.3	2	16.6	3	30
31 cases	+	10	83.3	2	16.6	0	0
	±	5	71.4	2	28.5	0	0
Secondary	++	18	63.1	28	36.8	9	18.9
135 cases	+	39	86.6	6	13.3	5	12.8
	±	13	92.8	1	7.1	1	7.6
Tertiary	++	1	10	6	60	2	50
22 cases	+	5	55.5	4	44.4	0	0
	±	3	100	0	0	0	0
Latent	++	11	70	6	30	2	14.2
37 cases	+	1	50	1	50	1	25
	±	9	100	0	0	1	11

Considering the cases giving a plus reaction the largest percentage of negative results occurred in the secondary stage, the smallest in the latent stage, while better results were obtained in the primary stage than in the tertiary. As regards relapses, none occurred in the primary or tertiary stages, while in the secondary stage 12.8 per cent. relapsed and in the latent cases 25 per cent.

Of the cases giving a plus-minus reaction the table shows that the best results were obtained, as regards the disappearance of the reaction, in the tertiary and latent cases, while the poorest results were obtained in the primary cases. As regards relapses none occurred in the primary or tertiary cases, but 7.6 per cent. relapsed in the secondary stage and 11 per cent. of the latent cases. In the cases in the tertiary and latent stage giving a plus-minus reaction the patients had received vigorous mercurial treatment before the administration of salvarsan, which undoubtedly explains the disappearance of the reaction in all of the cases. The patients who relapsed in the secondary stage had received no previous treatment, while the one patient who relapsed in the latent stage developed symptoms a few days after the reaction became negative.

From the data submitted it is evident that the intensity of the reaction in the various stages of the disease is of considerable prognostic import. Thus better results are obtained, as regards the disappearance of the reaction, in the primary cases giving a double-plus reaction than in the secondary, but the chances of a relapse are almost twice as great in the primary as they are in the secondary. It is also interesting to note that the plus-minus cases give a larger percentage of disappearances in

the secondary than in the primary stages of the disease, but that the chances of a relapse are greater in the secondary stage. The prognosis as regards the disappearance of the reaction and the occurrences of relapses, is most unfavorable in the tertiary cases which give a double-plus reaction.

#### RELATION OF THE METHOD OF ADMINISTRATION OF SALVARSAN TO THE DISAPPEARANCE OF THE COMPLEMENT FIXATION REACTION

I had hoped to be able to give some data regarding the relation of the dosage of salvarsan to the time of disappearance of complement fixation but in the cases analyzed the dosage has varied so little that no conclusions can be drawn regarding this phase of our subject.

The method of administration, however, had much to do with the disappearance of the reaction as will be seen on consulting Table 9. The methods used in the cases reported were as follows: Injection of the neutral suspension of the drug, intramuscular injection of the alkaline solution, intravenous injection, and combined intramuscular and intravenous injections.

TABLE 9—VARIOUS METHODS OF ADMINISTRATION OF SALVARSAN IN RELATION TO THE DISAPPEARANCE OF COMPLEMENT FIXATION IN LUES

Method of Administration	No of Cases	Became Negative	Per cent	Remained Positive	Per cent	Relapse	Per cent
Neutral suspension	9	7	77.7	2	22.2	5	71.4
Alkaline Sol. Intramuscular	150	118	78.6	32	21.3	8	6.7
Intravenous	30	16	53.3	14	46.6	6	37.5
Combined Intramuscular and Intravenous	36	23	63.8	13	36.1	5	21.7
Totals	225	164	72.8	61	27.1	24	14.6

*Neutral Suspension*—The neutral suspension of salvarsan was used in nine cases, of which seven became negative and five relapsed. Thus while the percentage becoming negative was quite large, the percentage of relapses (71.4 per cent) was enormous. It must be admitted that, as a rule, small doses were used, varying from 0.3 gm. to 0.5 gm., but even taking this into consideration it is evident that the method gives poor results when compared with any of the others mentioned. In justice to the method, however, it should be stated that the two cases which did not relapse, are still negative after a period of nearly ten months.

*Intramuscular Injection*—The intramuscular injection of the alkaline solution of salvarsan gave the best results, as regards the disappearance of the complement fixation test, in the cases which are here analyzed. Of the 150 cases so treated 78.6 per cent became negative, of which only 6.7 per cent relapsed, and as some of the cases which remained positive have only been observed for a period of four weeks it

is probable that the percentage of disappearance will become greater within the next two or three weeks, but this may also be true as regards the percentage of relapses. The dose of salvarsan varied from 0.5 gm to 0.6 gm.

*Intravenous Injection*—The intravenous method was used in thirty of the cases reported, of which 53.3 per cent became negative and 37.5 per cent relapsed.

Seven of the cases were given 0.5 gm of salvarsan, repeated in one week, and of these six became negative, one stayed positive and one relapsed. Four were given 0.6 gm once only, of which one became negative and four remained positive. Nineteen were given 0.5 gm once only, of which nine became negative, ten remained positive and five relapsed. The best results were obtained with two intravenous injections given one week apart.

*Combined Intramuscular and Intravenous Injections*—This method was used in thirty-six cases, of which 63.8 per cent became negative and 21.7 per cent relapsed, thus giving better results than the intravenous alone, but not as good as the intramuscular method. The dosage employed in the combined method was as follows: 0.2 gm intramuscular + 0.4 gm intravenous, 0.3 gm intramuscular + 0.3 gm intravenous, and 0.6 gm intramuscular + 0.3 gm intravenous. The best results were obtained with the latter dosage, 50 per cent of the ten cases so treated becoming negative, none of which have relapsed.

A few patients were treated with an intravenous, followed by an intramuscular, injection, but the number is too small to warrant any conclusions regarding the efficacy of this method of treatment.

The period intervening between the administration of the drug by the several methods and the disappearance of the reaction is given in Table 10.

TABLE 10—THE TIME OF DISAPPEARANCE OF THE COMPLEMENT FIXATION REACTION AFTER TREATMENT WITH SALVARSAN BY VARIOUS METHODS

Method of Administration	No of Cases	Date of Disappearance in Weeks							
		1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
Neutral suspension	7	1	4	2	0	0	0	0	0
Alkaline sol intramuscular	118	12	31	27	18	14	12	3	1
Intravenous	16	3	9	3	1	0	0	0	0
Combined intramuscular and intravenous	23	1	3	5	8	3	2	1	0
Totals	164	17	47	37	27	17	14	4	1

This table is of interest as showing the relative rapidity of the disappearance of the reaction after the several modes of treatment. It will be observed that the reaction disappeared less rapidly when intra-

muscular injections were used than when the drug was given intravenously. The great differences in the rapidity of the disappearance of the reaction after treatment with salvarsan are due to numerous factors, some of which are capable of explanation, while others are still unsolved. The situation of the spirochetes, the rate and amount of absorption of the drug and the character and severity of the infection, must all have something to do with the time of disappearance, while the existence of strains of spirochetes, which may be more or less resistant to the drug, a question still undecided, may also explain the slow disappearance of the reaction in certain cases. If, as Ehrlich believes, the fixation reaction may be produced by tissue changes which occur in answer to irritation brought about by the destruction of the spirochetes, it is easy to explain the delayed disappearance of the reaction by a slow elimination of these irritating products. When elimination is rapid, either because the amount of irritating substance is small, or the tissues concerned in elimination are very active, the reaction will disappear quickly, while, if the contrary is true, elimination will be slow and the reaction will persist for a considerable period.

In the intravenous injections twelve of the sixteen negative cases became so within two weeks, while the longest period from the time of the administration of the drug to the disappearance of the reaction was one month. One would naturally expect that the reaction would disappear more rapidly after intravenous injections than after intramuscular and this is borne out by our data. The fact remains, however, that some of these cases did not become negative for three or four weeks, and it is difficult to explain this on any other assumption than that the persistence of the reaction was due to the slow elimination of substances derived from the dead spirochetes or produced by the reaction of the tissues to them. When the drug is given by the intramuscular method it is absorbed slowly, exerting its action for days or perhaps weeks and killing the spirochetes by "the instalment plan" as it were, whereas when it is given intravenously it is absorbed and eliminated rapidly, and any destructive action on the spirochetes must occur in a comparatively short time. In the first case the elimination of the substances which Ehrlich believes have to do with the production of the reaction is gradual, because the spirochetes are being continually destroyed, whereas in the second cases these substances will be eliminated more rapidly because the parasites are all killed within a comparatively short time. The elimination may take some weeks even when the drug is given intravenously, but it will never take so long as when it is given by the intramuscular method other things being equal. This theory would appear to be contradicted by the results obtained in the cases treated with the neutral suspension, but these cases were very few in number and, therefore, of little value as an argument against the theory.

## RELATION OF PREVIOUS MERCURIAL TREATMENT TO THE DISAPPEARANCE OF COMPLEMENT FIXATION AFTER SALVARSAN

Previous treatment with mercurials has considerable effect on the disappearance of the complement fixation reaction after treatment with salvarsan. This is especially noticeable during certain stages of luetic infection and should always be considered in interpreting the results of various observers as regards this question. As a rule the reaction disappears more quickly in patients who have been subjected to mercurial treatment for some time than in those who have not, and the chances of relapse are less, although, as will be seen, relapses have occurred in patients previously well treated with mercury.

In the 225 cases reported 110 patients had received no treatment previous to the use of salvarsan. Of these eighty-two, or 74.5 per cent became negative, twenty-eight, or 25.1 per cent, remained positive, and ten or 12.2 per cent relapsed.

There were seventy-five cases in which a definite history of mercurial treatment was obtained before salvarsan was administered. Of these sixty-three, or 84 per cent, became negative, twelve, or 16 per cent, remained positive, and seven, or 9.3 per cent, relapsed.

From these figures it is evident that better results were obtained in the patients who had previously had mercurial treatment, for not only a larger proportion of the cases became negative, but a smaller proportion relapsed.

The relation of the stage of the disease in patients who had not received previous mercurial treatment to the disappearance of the reaction after salvarsan is shown in Table 11, while in Table 12 is shown the relation of the stage of the disease to the disappearance of the reaction in the patients who had received previous mercurial treatment.

TABLE 11—THE RELATION OF THE STAGE OF LUES TO THE DISAPPEARANCE OF THE COMPLEMENT FIXATION TEST AFTER TREATMENT WITH SALVARSAN IN PATIENTS WHO HAD RECEIVED NO PREVIOUS MERCURIAL TREATMENT

Stage of Disease	No of Cases	Became Negative	Per cent	Remained Positive	Per cent	Relapsed	Per cent
Primary	27	22	81.4	5	18.5	2	9
Secondary	67	48	71.6	19	28.3	8	16.6
Tertiary	8	5	62.5	3	37.5	0	0
Latent	8	7	87.5	1	12.5	0	0
Totals	110	82	74.5	28	25.4	10	12.2

In the primary stage, in patients previously untreated, twenty-two, or 81.4 per cent, became negative, while two, or 9 per cent, relapsed, as shown in Table 11. In none of the primary cases were the patients

given mercurial treatment prior to the administration of salvarsan, so that this column remains empty in Table 12

TABLE 12—THE RELATION OF THE STAGE OF LUES TO THE DISAPPEARANCE OF THE COMPLEMENT FIXATION TEST AFTER TREATMENT WITH SALVARSAN IN PATIENTS WHO HAD RECEIVED PREVIOUS MERCURIAL TREATMENT

Stage of Disease	No of Cases	Became Negative	Per cent	Remained Positive	Per cent	Relapsed	Per cent
Primary	0	0	0	0	0	0	0
Secondary	44	39	88.6	5	11.3	5	12.8
Tertiary	13	8	61.5	5	38.4	0	0
Latent	18	16	88.8	2	11.1	2	12.5
Totals	75	63	84	12	16	7	9.3

There were sixty-seven patients in the secondary stage of the disease who had not received mercurial treatment before salvarsan was administered. Of these 71.6 per cent became negative and 16.6 per cent relapsed. There were forty-four cases in the secondary stage which had received previous mercurial treatment, of which 88.6 per cent became negative, while 12.8 per cent relapsed. It is thus evident that better results were obtained in the secondary stage of the disease in the cases which had previously had mercurial treatment.

Eight patients in the tertiary stage who had not received previous mercurial treatment were tested, of the cases 62.5 per cent became negative, while none relapsed. Thirteen patients in the same stage of the disease, which had received mercurial treatment, were tested, of which 61.5 per cent became negative, none of which relapsed. Though the figures show a slight increase in the percentage of negative results in the untreated patients I believe that this is only apparent and that if the same number of patients in both classes had been treated the results would have been in favor of those who had received previous mercurial treatment.

Considering the latent infections eight patients were tested who had received no previous mercurial treatment, of these 87.5 per cent became negative and none relapsed, while of eighteen patients who had received previous mercurial treatment 88.8 per cent became negative and 12.5 per cent relapsed. The two patients who relapsed had previously had severe lesions which were quiescent at the time the patients were treated while in the patients who had received no mercurial treatment the histories show that the infection was of mild character. I do not believe that any conclusions can be drawn from the fact that relapses occurred in the patients treated with mercury, while none occurred in the untreated patients.

The time of disappearance of the reaction after treatment with salvarsan in various stages of the disease in patients given previous mercurial treatment and in those who had not received such treatment is shown in Tables 13 and 14.

TABLE 13—THE TIME OF DISAPPEARANCE OF THE COMPLEMENT FIXATION TEST AFTER TREATMENT WITH SALVARSAN IN PATIENTS WHO HAD RECEIVED NO PREVIOUS MERCURIAL TREATMENT

Stage of Disease	No of Cases	Date of Disappearance of Test in Weeks							
		1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
Primary	22	2	12	3	3	1	1	0	0
Secondary	15	6	11	13	6	4	6	1	1
Tertiary	5	1	2	1	0	1	0	0	0
Latent	7	1	1	1	1	2	1	0	0
Totals	52	10	26	18	10	8	8	1	1

A comparison of these tables shows that there is little difference in the rate of disappearance of the reaction in either class of patients. This fact is of interest as it supports the theory that the time of disappearance depends on the rate of elimination of the substance or substances derived from the dead spirochetes or produced by the reaction of the tissues to them, the slight difference in favor of the previously treated patients being due to the destruction of a portion of the parasites, prior to the administration of salvarsan.

TABLE 14—THE TIME OF DISAPPEARANCE OF THE COMPLEMENT FIXATION TEST AFTER TREATMENT WITH SALVARSAN IN PATIENTS WHO HAD RECEIVED PREVIOUS MERCURIAL TREATMENT

Stage of Disease	No of Cases	Date of Disappearance of Test in Weeks							
		1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
Primary	0	0	0	0	0	0	0	0	0
Secondary	39	4	10	10	8	5	2	0	0
Tertiary	8	1	3	3	0	0	1	0	0
Latent	16	0	5	3	4	2	2	0	0
Totals	63	5	18	16	12	7	5	0	0

The relative efficiency of salvarsan and mercury in causing a disappearance of the fixation reaction is strikingly illustrated in the cases of patients who had previously received mercurial treatment. Of fifty-three patients who were treated with mercury by the mouth for nine months or more before the administration of salvarsan and who gave a positive Wassermann reaction, all became negative within eight weeks after the administration of this drug. The intensity of the reaction in

these cases is shown in Table 15, together with the time of previous mercurial treatment

TABLE 15—THE RESULTS OF THE COMPLEMENT FIXATION TEST IN FIFTY THREE PATIENTS WHO HAD RECEIVED MERCURIAL TREATMENT BEFORE THE ADMINISTRATION OF SALVARSAN

Method of Treatment	Time of Treatment	No of Cases	Character of Reaction		
			++	+	±
Internal	9 months	17	8	7	2
Internal	1 year	19	11	6	2
Internal	2 years	11	3	7	1
Internal	3 years	6	2	3	1
Totals		53	24	23	6

It will be observed from a consideration of Table 15 that nineteen of the patients had received mercury internally for one year, of whom eleven still gave a double-plus reaction, that eleven had received internal treatment for two years, of whom three still gave a double-plus reaction, and that six patients had received internal treatment for three years, of whom two still gave a double-plus reaction, while the remainder gave a plus or a well-marked plus-minus reaction. Comparing these results with those obtained after the administration of salvarsan, all of the cases becoming negative within eight weeks, and in a vast majority of instances after only one injection of the latter drug, the infinitely greater specific action of salvarsan is clearly demonstrated.

It is generally admitted that the most efficient method of administering mercury is by the hypodermic injection of suitable salts of the metal. Ten of the patients in whom the complement fixation test was still positive had been treated in this manner before the administration of salvarsan and the number of mercurial injections and the intensity of the reaction was as follows

Two patients had received 7 injections and gave a double plus reaction  
 One patient had received 8 injections and gave a plus reaction  
 One patient had received 9 injections and gave a double plus reaction  
 One patient had received 11 injections and gave a double plus reaction  
 One patient had received 15 injections and gave a plus reaction  
 One patient had received 18 injections and gave a double-plus reaction  
 One patient had received 20 injections and gave a plus reaction  
 One patient had received 25 injections and gave a plus reaction  
 One patient had received 30 injections and gave a plus reaction

After one intramuscular injection of salvarsan the complement fixation test in all of these patients became negative and has remained so until the present time, most of them having been observed for from two to four months. While the previous mercurial treatment must have had some effect on the infections, perhaps rendering them more sensitive to the action of salvarsan, I think it must be admitted that the results amply demonstrate the superior specific action of the latter drug.



## DISCUSSION OF RELAPSES

It has been stated that of the 225 cases analyzed in this paper, twenty-four, or 14.6 per cent have relapsed. In order to understand the exact significance of these results it is necessary to consider the cases somewhat in detail<sup>10</sup>

First, as regards the relation of the stage of lues to relapses. In the primary stage three of the twenty-five cases which became negative, or 12 per cent, relapsed, in the secondary stage fifteen out of 100 cases, or 15 per cent, in the tertiary stage, two of twelve cases, or 16.6 per cent, and in the latent stage four of twenty-seven cases, or 14.8 per cent. It will thus be seen that the prognosis as regards relapses after treatment with salvarsan is best in the primary stage and most unfavorable in the tertiary, while it is better in the latent cases than in the secondary. Of course it is yet too early to conclude that no more relapses will occur in this series of cases, but the figures are correct, at least, as regards the occurrence of early relapses.

Second, the relation of the intensity of complement fixation to relapses. The complement fixation test gave a double plus reaction before treatment with salvarsan in sixteen of the twenty-four cases which relapsed, a plus reaction in six of the cases, and a plus-minus reaction in two of the cases. Therefore, the prognosis as regards relapse varies with the intensity of complement fixation, the best results being obtained in the cases giving a plus-minus reaction and the worst in those giving a double-plus reaction. This fact is of interest as it indicates that there is some relation between the intensity of complement fixation and the resistance of lues to treatment with salvarsan. That this is true is strikingly illustrated when one correlates the stage of the disease and the intensity of the reaction with the percentage of relapses. Thus, as is shown in Table 8, the relapses occurring in the primary stage of lues were all in patients giving a double-plus reaction, no less than 30 per cent of such patients relapsing, while no relapses occurred in patients giving a plus or a plus-minus reaction. The same is true in the tertiary cases, 50 per cent of the patients giving a double-plus reaction relapsing, while no relapses occurred in those giving a plus or a plus-minus reaction.

In the secondary cases the largest percentage of relapses occurred in patients giving a double-plus reaction, but relapses also occurred in cases giving a plus and a plus-minus reaction, the percentage decreasing with the severity of the reaction. An apparent exception to the rule is noted in the latent cases, where 25 per cent giving a plus reaction relapsed and only 14 per cent giving a double-plus reaction, but there were only four patients tested who gave a plus reaction while there were fourteen tested giving a double-plus reaction, so that it is probable that had the

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10 Since writing the above, the percentage of relapses has increased slightly

same number of patients in each class been tested the results would have been similar to those obtained in the other stages of the disease

Third, the relation of the method of administration of salvarsan to the occurrence of relapses. The percentage of relapses varying greatly with the method of administration of salvarsan

The neutral suspension of the drug was used in nine cases, of which seven became negative and five, or 71.4 per cent, relapsed. The alkaline intramuscular injection was used in 150 cases, of which 118 became negative and eight, or 6.7 per cent, relapsed. The intravenous method was used in thirty cases of which sixteen became negative and six, or 37.5 per cent, relapsed. The combined intramuscular and intravenous method was used in thirty-six cases, of which twenty-three became negative and five, or 21 per cent, relapsed. From these data it is evident that the intramuscular injection of the alkaline solution has given the best results as regards the occurrence of early relapses and the neutral suspension the poorest, while the combined intramuscular and intravenous has given better results than the intravenous method alone. It is also evident that the neutral suspension, as recommended by Wechsellmann, should be discarded as a method of administering the drug.

Fourth, the relation of previous mercurial treatment to relapses. A slightly smaller percentage of relapses occurred in the secondary cases which had received previous mercurial treatment than in those which had not, but I do not believe that any conclusions can be drawn from the data relating to this phase of the subject, as in the vast majority of cases the amount of mercurial treatment was small and apparently had but little effect as regards the occurrence of relapse. In the latent cases which had received previous mercurial treatment 12.5 per cent relapsed, while in those which had received no mercurial treatment relapses did not occur. A much smaller number of cases belonging to the latter class were tested, however, and therefore the results are untrustworthy and general conclusions cannot be drawn from them. (See Tables 11 and 12.)

#### THE TIME OF OCCURRENCE OF RELAPSES AFTER SALVARSAN

In considering this portion of our subject it should be remembered that I am only able to give the data concerning the relapses which have occurred in from one to six months after treatment and that the large majority of negative cases have only been observed for three months since the reaction became negative. It is more than probable that some of these cases will relapse later, but the results obtained indicate that the majority of relapses occur within eight weeks after the reaction becomes negative and that comparatively few occur after three months. Table 16 shows the time of occurrence of the relapses in the twenty-four cases under discussion, the time being given in weeks and computed from the date on which the complement fixation test became negative.

TABLE 16—TIME OF RELAPSE IN TWENTY-FOUR PATIENTS TREATED WITH SALVARSAN

Time of Relapse in Weeks	No. of Cases	Time of Relapse in Weeks	No. of Cases	Time of Relapse in Weeks	No. of Cases
4 weeks	2	9 weeks	1	16 weeks	1
5 weeks	4	10 weeks	1	22 weeks	1
6 weeks	3	11 weeks	2	23 weeks	1
7 weeks	4	12 weeks	2		
8 weeks	1	14 weeks	1		
	<hr/> 14		<hr/> 7		<hr/> 3

It is evident from the table that more than half of the relapses occurred within eight weeks after the reaction became negative and that twenty-one of the twenty-four patients relapsed within fourteen weeks. I believe that these results indicate that, in the vast majority of instances, a relapse will occur within six months if it is going to, and that if a previously positive Wassermann test remains negative for as long as a year after the administration of salvarsan, provided clinical symptoms are absent, a relapse will not occur. I realize that this opinion is contrary to that held by many, i. e., that several years must elapse before one can be sure that this drug really cures lues, but I believe that unless the spirochetes are destroyed clinical symptoms will appear or the complement fixation test will become positive within a year, provided mercurial treatment is withheld.

I think that most authorities would consider a patient as cured who had taken a course of mercurial treatment and whose blood gave a negative Wassermann reaction a year after the cessation of such treatment, and I can see no reason why the same standard should not hold good in the treatment of this disease with salvarsan. Indeed, the mere fact that one or two injections of this drug has been followed by as good results as three years' treatment with mercury, as regards the complement fixation test, should render this standard more conclusive in the case of salvarsan than in the case of mercury. I am aware that clinical relapses sometimes occur with a negative Wassermann reaction, but I am very sure that a patient showing neither clinical symptoms nor a positive Wassermann reaction within a year after treatment with salvarsan may be considered as cured of syphilitic infection. Exceptions may occur but they will be the exceptions which will prove the rule.

#### GENERAL CONCLUSIONS

From the analyses of complement fixation tests after the administration of salvarsan which are given in this paper I believe that the following conclusions may be safely drawn

- 1 The best results, as regards the disappearance of the complement fixation test and the occurrences of relapses, are obtained in the treatment

of patients in the primary stage of lues and the poorest in the treatment of those in the tertiary stage

2 The complement fixation reaction disappears somewhat more rapidly after treatment with salvarsan in the tertiary stage than in either the primary or secondary stage of the disease

3 The reaction in our experience has disappeared during the second, third and fourth weeks after treatment in the vast majority of the negative cases

4 The prognosis, both as regards the disappearance of the reaction and the occurrence of relapses, is most favorable in patients giving a plus-minus reaction and least so in those giving a double-plus reaction

5 As regards the method of administration of salvarsan the best results have been obtained, in our experience, from the intramuscular injection of the alkaline solution and the poorest from the use of the neutral suspension. In justice to the intravenous method, however, it should be stated that a smaller number of cases have been tested and it may be that this method will prove as efficient as the intramuscular

6 The complement fixation reaction disappears more rapidly after the intravenous administration of salvarsan than after the intramuscular administration

7 As regards the disappearance of the complement fixation reaction better results were obtained in patients who had previously received mercurial treatment than in those who had not, but the time of disappearance of the reaction was little affected

8 The great superiority of salvarsan over mercury, as a specific remedy, was shown in the rapid and apparently permanent disappearance of the reaction, after one or two injections of the drug, in patients previously treated for one, two or three years with mercurials and in whom the reaction had remained positive

9 The complement fixation test is of the very greatest value as a guide to treatment with salvarsan and it is the only method we possess of determining whether lues is actually cured by any therapeutic agent

Finally, I believe that the data recorded in this paper eloquently sustain Ehrlich's modest claim,<sup>11</sup> "that the introduction of '606' makes a considerable advance in the therapy of syphilis, an advance which is not due to accident, but to the result of systematic experimental work"

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11 Ehrlich, P. *Chemotherapy*, Ed 1, New York, 1911, p 127

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## THE IMPORTANCE OF TONUS FOR THE MOVEMENTS OF THE ALIMENTARY CANAL \*

WALTER B CANNON, M D

BOSTON

Four years ago, during an investigation of movements of the esophagus after total vagus section, I was struck by the difference between the primary and the secondary results of the operation. The primary result, seen during the first twenty-four hours after the esophagus is isolated from the central nervous system, is apparently a complete paralysis. Food, pushed onward by the still efficient cervical gullet, accumulates in a widely distending mass in the lower esophagus and may stagnate there for hours with no indication of any reaction of the encircling wall. In a few days, however, a remarkable recovery of function occurs in the lowest part of the tube, which is provided with smooth muscle. Contraction and peristalsis now appear in this region when food accumulates. An important factor for arousing these activities seems to be the stretching of the esophageal wall. For example, in the first days of recovery, a slender mass spread along the tube may lie for some time unmoved, the addition of a second mass, which causes further distention of the wall, results instantly in contractions and peristalsis. And similarly after some of the food has been driven into the stomach, the strand that remains, now reduced to a slender mass again, lies for long periods without arousing any movements of the gullet. As days go by, the lower thoracic esophagus becomes more responsive to the presence of contained material, for the material is forced into the stomach with increasing rapidity, and even slender masses are now sufficient cause for peristalsis.<sup>1</sup>

What is true of the lower thoracic esophagus is also true of the stomach. If the splanchnic nerves are severed (in the cat), the normal movements of the gastro-enteric canal are not altered. If now the vagus nerves are cut, the immediate result is defective functioning. For twenty-four hours after isolating the stomach from the central nervous system,

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\*From the Laboratory of Physiology in the Harvard Medical School

\*Presidential address delivered before the American Gastro-Enterological Association, April 19, 1911

1 Cannon. *Am Jour Physiol*, 1907, *ix*, 441

the discharge of food is much retarded. Later there is a recovery of almost normal activity.<sup>2</sup>

A suggestion of the condition which makes possible the restoration of peristalsis in both the isolated esophagus and the stomach was found at autopsy of animals killed two weeks after total vagus and splanchnic section. The stomach was found in remarkable tonic contraction.<sup>3</sup> In two instances the diameter through most of the length ranged between 1.5 and 2 cm—a smallness of size almost incredible when compared with the diameter of the stomach filled with food. The question at once arose as to whether this tonic contraction was not in fact fundamental to the rhythmic movements.

This suggestion was first tested by injecting material into the stomach when that organ was in different degrees of contraction. If the abdomen is opened under warm normal salt solution, sometimes the empty stomach is found large and flabby, with collapsed walls, at other times it is small and contracted. Under these different circumstances the injection of a mushy mass has quite different effects. The flabby stomach simply gives way before the pressure of the injected material, without any reaction, the tonically contracted stomach, on the other hand, begins, as soon as sufficiently distended, to exhibit peristaltic waves.

The importance of the tonic state is further attested by injecting into a vein a small dose of epinephrin (P. D. & Co.) while the gastric peristaltic waves are running. This produces complete relaxation of the stomach and a cessation of peristalsis. The pressure on the stomach contents (which measures the tonus of the neuromusculature) falls to zero. A careful record of the movements of the gastric wall in the pyloric end, with simultaneous record of intragastric pressure, shows that the pressure begins to rise in the stomach, i. e., the tonic state begins to be established, before peristaltic waves begin to travel towards the pylorus.

The importance of tonus to rhythmic activity can be demonstrated also with the excised stomach. If an inactive stomach is removed from the body, is filled with warm water, is tied at the two ends, and placed in warm oxygenated Ringer's solution, it usually shows no sign of peristalsis. If, now, a small amount of barium chlorid is added to the Ringer's solution, the stomach becomes tonically contracted and peristaltic waves are generated.

The foregoing observations on the relation of tonus and peristalsis in the stomach are amplified and elucidated by an examination of these relations in the colon. All investigators who have studied antiperistalsis

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<sup>2</sup> Cannon. *Am Jour Physiol*, 1906, *vii*, 437.

<sup>3</sup> "Tonus" is used in this paper to designate a state of more or less persistent shortening of the circular muscle of the alimentary canal.

of the colon have noted that the waves start from the narrow constriction, or tonic ring, nearest the cecum, but the part played by this ring has been overlooked. Two years ago I reported that by producing a tonic ring in the proximal colon (exposed under warm normal salt solution), either by pinching or by applying a weak solution of barium chloride, moving waves could be made to appear at will. A ring at the cecum repeatedly sends off downward-running waves, a new ring made now near the terminus of these waves starts reversed waves, and a tonic ring made midway in the proximal colon not infrequently will originate waves which pass away in both directions. These phenomena occur not only in the large intestine connected with the body, but also in the excised colon. The phenomena of the tonic ring are therefore of prime importance in explaining the occurrence of antiperistalsis of the colon and possibly also the similar peristalsis of the stomach.

The antiperistalsis of the colon and the peristalsis of the stomach are alike in presenting a series of waves following one another in rhythmic succession. They must, therefore, have a source that is rhythmically active. Careful inspection of the exposed colon over which antiperistaltic waves are passing reveals the interesting fact that the tonic ring, from which they start, pulsates, and that each pulsation sends away a moving ring of constriction.

The pulsations of the tonic ring and the discharge of waves from it are dependent on a state of tension. Thus if, while the waves are running from a ring, the fluid contents are largely withdrawn, visible waves cease. Reintroducing the fluid starts the waves again. The observation which I reported in 1901, that antiperistalsis begins whenever new material is pushed into the colon from the ileum, agrees completely with the experimental evidence that distention of the intestine is the condition for the appearance of the waves.

Mechanical stretching is well recognized as a most efficient stimulus for exciting activity in smooth muscle. The evidence already cited for the esophagus, stomach and colon, is supported by similar observations on the small intestine,<sup>4</sup> ureter<sup>5</sup> and bladder.<sup>6</sup> Since smooth muscle surrounds hollow organs, which gradually fill and must be emptied, the value of distention as a stimulus is obvious.

The extension of smooth muscle which evokes a contraction must not, however, be merely the elongation of non-elastic substance. This is a point which I wish especially to emphasize. When an organ with walls of smooth muscle is flaccid and toneless, distention calls forth no response. As already noted, such is the case in the isolated esophagus

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<sup>4</sup> Bayliss and Starling. *Jour. Physiol.*, 1901, xxvi, 134.

<sup>5</sup> Sokoloff and Luchsinger. *Arch. f. d. ges. Physiol.*, 1881, xxvi, 467.

<sup>6</sup> Guyon. *Compt. rend. Soc. de Biol., Paris*, 1900, lii, 712.

and stomach immediately after severance of the vagus nerves, such is the case in the rectum<sup>7</sup> and bladder<sup>8</sup> immediately after the nerves have been cut which supply them with tonic impulses, such is the case also in the atonic colon. I have repeatedly attempted to call forth rhythmic contractions both in the atonic stomach and in the atonic colon, by distention, but without success. Only when the muscle is shortened and resilient, i. e., in a state of tonus, does stretching result in a contraction. The tonic state, therefore, is quite as important as the internal pressure—indeed, it is the condition for the existence of that pressure. And when stretching is said to be the efficient stimulus for rhythmic contraction of smooth muscle, the statement implies that the muscle is in a condition to be *stretched*.

Moderate loads applied to smooth muscle extend it more when it is in a short state than when it is in a long state.<sup>9</sup> At the tonic ring of the colon, therefore, the neuromusculature, because shortened, is especially subject to distention by internal pressure. And being in a tonic state, it will respond by contraction.

A single contraction in a rhythmic series consists of almost symmetrical stages of shortening and relaxation. During the stage of shortening and the first part of the stage of relaxation there is evidence that the neuromusculature of the alimentary canal is relatively refractory to stimulation.<sup>10</sup> When the tonic ring, therefore, begins to contract in response to distention, it becomes non-irritable to the stimulus, i. e., to the internal pressure. It begins again to be subject to this stimulus after having reached its most contracted state and having become partly relaxed—when again readily distensible. Now on being distended by the internal pressure, the ring is stimulated and, as before, responds by contraction. Thus the neuromusculature in a tonic state responds to a distending pressure by contraction, and the refractoriness which develops during the contractile phase and the lessened irritability during relaxation assure a rhythmic response. These factors can all be reasonably invoked to explain the pulsations of the tonic ring.

The spread of the contraction from the pulsating ring along the intestine, as a wave, is probably another instance of a widely observed phenomenon in simple neuromuscular structures, the passage of the state of excitation from a contracted region to a stretched region.<sup>11</sup> Evidently a contraction of the tonic ring must increase internal pressure on neighboring parts of the intestinal wall. If these neighboring parts

7 Elliott and Barclay-Smith Jour Physiol, 1904, *xxvi*, 289

8 Elliott Jour Physiol, 1907, *xxxv*, 424, 425

9 Schultz Arch f Physiol, 1903, Suppl, p 25

10 Ducceschi Arch per l Sci Med, 1897, *xxi*, 170, Magnus Arch f d ges Physiol, 1904, *ciii*, 540, 1906, *cxi*, 152

11 See von Uexküll Ergebn d Physiol, 1904, *iii*, 4



are in tonic contraction, they are thereby set in increased tension. Then the distended area, the muscle rings of this area begin to contract and thus either independently, as a result of extra stretching, or because the excitation, which is manifested in pulsation of the ring, spreads into the freshly to distend the regions beyond. The wave thus passes from the pulsating ring to inactive regions of the intestine, and since the constriction trails behind it an area of lessened irritability it cannot return on its course but must always move away from its place of origin.

The precise relation between the degree of tonus and the internal pressure that results in rhythmic contraction, is difficult to define. When a tonic ring is first made in the colon, it is a deep and strong contraction and it manifests no evidence of pulsations. Only when it has to some extent relaxed does it begin to beat rhythmically. On the other hand, if the internal pressure is sufficiently increased, the waves moving along the intestine will disappear and can be seen again only when the distention is reduced. Both the tonus and the distending force, therefore, can be too great for rhythmic action.

From the foregoing evidence and discussion, it is clear that, given the state of tonus in the neuromusculature of the colon, and a locally increased tonic contraction opposing an internal pressure, the characteristic antiperistalsis can be explained. As already stated, gastric peristalsis has many features in common with colonic antiperistalsis. Can the same principles be applied to explain the rhythmic gastric movements?

The stomach when first filled has roughly a conical shape—the circumference is large at the cardiac end and progressively smaller as the pylorus is approached. If the contents are fluid or semifluid, and are subjected to the tension of the gastric musculature, the pressure throughout the contents (gravity aside) will be uniform. Every unit area of the wall will be supporting the same pressure. Obviously, then, a circumference of given width in the larger cardiac end will be subjected to greater total stress than a circumference of equal width in the smaller pyloric end.

Since the forces in the inactive stomach are in equilibrium, however, the encircling muscle of the cardiac end necessarily has to exert stronger tension than that in the pyloric end. And furthermore, since the muscular wall of the cardiac sac is thinner than that of the vestibule, there are fewer muscle fibers in equal cross-sections. The greater circumference and the weaker musculature both tend to place the cardiac region at a disadvantage. The tension of the muscle in this region, therefore, must determine the pressure in the stomach.

The necessity of tone as a condition for gastric peristalsis, and the existence of a tonic state during digestion (as shown by intragastric pres-

sure) have already been mentioned. The application to the stomach of the factors used to account for the rhythmic contractions of the colon involves first of all a consideration of the degrees of relation between tonus and internal pressure. As noted in the discussion of the activities of the colon, the internal pressure may be too slight to stimulate the tonically contracted muscle, or it may be too great. Because of the conical shape of the stomach it is quite possible for a pressure to be produced too great for the neuromusculature of the distended cardiac end and too little for that of the pyloric end. Between the large cardiac and the small pyloric ends, however, the relations between internal pressure and tonus will be intermediate, and at some point the relations will be suitable for a contractile response. The material displaced by a contraction must be accommodated in the cardiac region where the weakest muscles are working against greatest obstacles. As the contracted band relaxes, however, the tonic pressure from the cardiac end again puts it on a stretch. Thus the contraction would be repeated rhythmically at this point, for the same reasons that were given for rhythmic pulsations of the tonus ring in the colon.

Each pulsation of the adapted gastric band will send off a wave toward the pylorus. The wave will not travel in the opposite direction (towards the fundus), because the cardiac sac is too much stretched to respond, if it were not, it would itself be the site of the pulsating band.

In harmony with the preceding argument is the observation that when peristaltic waves are running on the stomach, their place of origin can be shifted towards the pylorus by increasing internal pressure, or almost to the fundus by decreasing that pressure. In the first procedure the overstretched region is extended and the pulsating circumference, having to meet a greater distending force, is moved to a region where the muscles are stronger and lie in a smaller ring. In the second procedure precisely the opposite occurs—the muscles of the cardiac end, gradually less stretched beyond their responding power, begin to contract and in consequence the pulsatile source of the waves is moved farther towards the area of weakest musculature and longest circumference.<sup>12</sup>

As the stomach empties, the mid-region becomes narrow. The waves then originate at the upper end of a gastric tube, at a pulsating ring which separates the tube from the cardiac sac. The ring forms a depression which has been repeatedly noted in x-ray photographs of the human stomach,<sup>13</sup> and is observable also in the exposed stomach of lower animals. In radiographs this persistent constriction has been designated the

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<sup>12</sup> Cannon. *Am Jour Physiol*, 1911, xxvii, p. viii.

<sup>13</sup> See Kaestle, Rieder and Rosenthal. *Arch Rontgen Ray*, 1910, xv, 21-24.

'*incisura cardiaca*.' The activity of this deepened ring can best be explained in the same terms that were used to explain the activities of the tonic constrictions of the colon.

Since the stomach when full has a conical shape, the formation of a gastric tube of fairly uniform diameter requires a greater contraction at the cardiac end of the tube than at the pyloric end. Because the cardiac incisure, at the extreme cardiac end of the tube is therefore more contracted than any other part of the stomach, it, like the tonic ring in the colon, is probably more easily distended than any other part. Distention by internal pressure causes the tonic ring to respond rhythmically. Each contraction sends off a wave towards the pylorus. And as the food is forced on into the intestine, the cardiac sac, by tonically pressing on its contents, provides more material for the waves, while helping to maintain the internal pressure necessary for the continuance of gastric peristalsis. Only after the contents, the medium for exercising internal pressure, have disappeared, does gastric peristalsis normally cease.

Distention of a tonically contracted neuromusculature explains not only the rhythmic activities of the stomach and colon, but also those of the small intestine. The contractions of the intestine can be increased, within limits, both in extent and vigor by an increase in the distending force, or if the contractions are absent they may be started by distention<sup>14</sup>. When a distending balloon is introduced into the intestine, the contractions are most marked in the region of greatest tension<sup>15</sup>. The violent segmenting activity in cases of obstruction<sup>16</sup> also point to distention of the gut as a cause of rhythmic contractions. Indeed rhythmic segmentation itself is an excellent example of the response of the intestine to stretching, for the contraction each time occurs in the bulging region, about midway between two previous contractions<sup>17</sup>.

In the esophagus, the stomach, the colon, and the small intestine, the importance of tonus has now been explained. It is the prime condition for that tension, or stretching, which has long been recognized as the most effective means of rousing contraction in viscera with walls of smooth muscle. When that tension is developed, contraction results, and if the tension persists, the contraction recurs. It recurs as soon as the neuromusculature can recover from a previous contraction. The result is that *rhythmic* activity appears—the activity most obviously characteristic of all movements of the alimentary canal. Since, therefore, the tonic state underlies all these exhibitions of rhythmicity, it is important to consider the conditions under which tonus is developed.

14 Bayliss and Starling Jour Physiol, 1899, xxiv, 105

15 Bayliss and Starling Jour Physiol, 1901, xxvi, 134

16 Cannon and Murphy Am Surg, 1906, xlii, 522

17 Cannon Am Jour Physiol, 1901, vi, 256

When the vagus nerves are cut, the movements of the esophagus and stomach are for some time in abeyance, and even when peristalsis reappears the constrictions at first are weak and relatively ineffective. On the other hand, repeated stimulation of the vagus nerves causes an increased and more permanent tonic contraction of the gastric wall, and as the tonus increases the peristaltic constrictions increase in vigor.<sup>18</sup> We may conclude, therefore, that the function of the vagi is that of setting the neuromusculature in a tonic state, of making it exert a tension, so that in relation to the contents it acts as if stretched by those contents.

The evidence already adduced to show the importance of the tonic state for normal functioning is reinforced by the observation previously mentioned that when all extrinsic nerves are cut, the esophagus and the stomach develop in time, within themselves, a tonic state. Whether the vagi are present or not, therefore, the neuromusculature must be in tonus and in tension before response will occur. In all probability the vagi adapt the size of the stomach to the varying amount of food ingested. Thus, if the stomach were relaxed, these nerves might set the musculature into tension about a small amount of food which would not by itself produce any tension whatever. When these nerves are severed, however, and time is allowed for the development of an autogenic tonus, the autogenic tonus compensates by rendering the stomach so contracted that even if a small amount is swallowed the muscle is stretched and peristaltic activities are at once started.

The question now arises as to the stage in the digestive process at which vagus influences affect gastric tonus. That impulses pass down the vagus nerves to the stomach during mastication and ingestion of food was proved by Pawlow's observation on the psychic secretion of the gastric juice.<sup>19</sup> As already stated, repeated stimulation of the vagi results in an increased tonic state which is much more persistent than that which follows single stimulation. Since a tonic state is necessary for gastric peristalsis, and since, as we have seen, peristalsis does not appear if the vagi are cut shortly before food is eaten, the inference is that, just as there is psychic secretion, so also there is psychic tonus. At present, however, no direct evidence for this inference has been secured.

After digestion is well started, the vagus nerves can be severed without altering either the nature of gastric peristalsis or the rate at which the stomach empties itself. This statement is based on observations by means of x-rays, also on inspection, and on records of intragastric pres-

<sup>18</sup> May Jour. Physiol., 1904, xxxi, 262

<sup>19</sup> Pawlow The Work of the Digestive Glands, London, 1902, p. 50

sure when the digesting stomach was exposed under salt solution. The initial tonus (psychic?) might be aroused while food was being ingested, and might continue for a period of some minutes thereafter. Then the tonic state must be maintained by other agencies. As the above evidence, together with observations on the excised stomach, shows, the tonic state, once established at the beginning of gastric digestion, is self-supporting. And again like the psychic secretion, it maintains itself by some local mechanism.

The small intestine is also supplied with "motor" impulses by the vagus nerves. Stimulation of these nerves, in the absence of the splanchnics, results in a brief inhibitory phase, followed by a rise of tonus and a gradual increase of rhythmic contractions to an extent above the normal.<sup>20</sup> In all probability, therefore, the vagi act on the intestine, just as they act on the stomach, to produce a tonic condition of the neuromusculature. In this connection it is interesting to recall Magnus' experience in studying isolated pieces of intestine, that the strips beat more actively when removed from a normally-fed animal than when removed from an animal that was not digesting.

The tonus of the colon is increased by the pelvic visceral nerves which belong to the sacral autonomic system. They are distributed especially to the distal part of the colon. Nevertheless, Elliott and Barclay-Smith report that stimulation of these nerves first increases the tone of the mid-region of the large intestine, and that then antiperistaltic waves may arise in the region of increased tone.<sup>21</sup> Severance of these nerves causes evident disturbance of the movement of the colon. The loss of the tonic impulses results in accumulation of feces, and in weak and sluggish contractions just as is the case when the vagus impulses are removed from the esophagus and stomach.

Looking back over the evidence here adduced we see that double provision is made for the establishment of a state of tonic contraction in the alimentary neuromusculature. Almost the entire length of the digestive canal is supplied with extrinsic nerves which when stimulated cause an increase of tone and when destroyed leave the canal at first in a toneless state. And if the canal is entirely separated from the central nervous system it has a remarkable power of developing an independent tonic state. When thus isolated, the canal regains its characteristic movements only as it recovers tone. Tonus is therefore fundamental. It supplies the resiliency that causes the state of tension when the canal is filled, or establishes the state of tension when the canal is only partly filled. The state of tension is the occasion for the contraction of viscera which

20 Bayliss and Starling *Jour. Physiol.*, 1899, **xiv**, 131

21 Elliott and Barclay-Smith *Jour. Physiol.*, 1904, **xxi**, 282, 283

are walled with smooth muscle holding a nerve net. Refractoriness to stimulation during contraction, and gradually increasing irritability during relaxation, result in a rhythmic response to the condition of tension. The most characteristic feature of the movements of the alimentary canal, their rhythmicity, can thus be accounted for.

The view that tonicity of the neuromusculature of the alimentary canal is a fundamental necessity for the appearance of rhythmic movements harmonizes many diverse observations. It accounts for the failure of efficient motility in atonic states of the stomach and intestines. It gives a reasonable explanation for the existence and importance of extrinsic motor nerves. It is in agreement with the observation that tonic contraction and rhythmic peristalsis disappear together in cases of general bodily weakness, when the depleted central nervous system may be supposed to fail to deliver the necessary tonic impulses, it is also in agreement with the observation that worry, anxiety and distress stop gastro-intestinal movements, for such states, accompanied by splanchnic impulses, abolish tonus. It fits admirably with the fact that the stomach of hungry animals is strongly contracted, for then the tonic state makes the organ ready for instant action on swallowed food. Indeed I am inclined to believe, for reasons which time does not now permit me to develop, that the sensation of hunger results from tonic contraction of the empty stomach. These are only some of the conditions in which the importance of tonus for movements of the alimentary canal is manifested, doubtless other conditions will suggest themselves.

240 Longwood Avenue

# BRILL'S SYMPTOM-COMPLEX, TYPHUS FEVER, MAN- CHURIAN TYPHUS

G A FRIEDMAN, M D  
NEW YORK

In 1910 Dr Nathan E Brill<sup>1</sup> published a clinical study based on 221 cases of a disease which he has observed during the last fourteen years in the wards of Mount Sinai Hospital. His definition of the disease in question is as follows: An acute, infectious disease of unknown origin and pathology, characterized by a short incubation period (four to five days), a period of continuous fever, accompanied by intense headache, apathy and prostration, a profuse and extensive erythematous maculopapular eruption, all of about two weeks' duration, whereupon the fever abruptly ceases either by crisis within a few hours or by a rapid lysis within three days, when all symptoms disappear.

Although these cases have been taken for typhoid fever by the greater number of New York physicians, yet there is no question that Brill is right in emphatically stating that this is an incorrect interpretation of the symptom-complex described. He publishes a tabular arrangement of the differences in the clinical pictures of the two diseases, which is quite convincing, more important yet is the fact that in none of the 221 cases observed was a Widal agglutination reaction obtained, and blood-cultures carried out under the supervision of Dr E Labman of the Mount Sinai Hospital were uniformly negative. Similar reasoning proves that the disease under discussion has nothing in common with the group of paratyphoid diseases, for in these also agglutination reactions and specific organisms have not been obtained. A committee of the Section of Medicine of the New York Academy of Medicine appointed to consider Brill's communication has agreed with Brill on these points.

Brill then considers the differentiation of his symptom-complex from typhus fever, the resemblance to which he admits, saying that "I should have felt that I had offered nothing to our nosology if it had not been proved that typhus fever had lost its virulence, that it was constantly present in a community, that it was not communicable, that when it was present epidemics of it did not occur, and that it was no longer a grave and fatal disease." "But," he adds, "with typhus fever as the great

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\*Read before the Section on Medicine, New York Academy of Medicine, May 16, 1911.

1 Brill, Nathan E. An Acute Infectious Disease of Unknown Origin, *Am Jour Med Sc*, 1910, p 484.

masters of medicine have taught and as I have seen it, such a conception would be unjustifiable, therefore, I believe this disease not to be typhus fever”

It is my purpose to show in this paper that the conditions which Brill demands as the *sine qua non* of admitting that his clinical entity is typhus fever can be proved to exist, and that the disease in question is in no way different from a great number of typhus fever cases observed during epidemics in countries in which typhus fever is endemic or from sporadic cases observed in the United States and elsewhere. With all deference to the great masters of medicine who have differentiated typhus and typhoid fevers and have given us the typical description of the former disease, which description has been repeated constantly since in the textbooks of countries where typhus fever is unknown or unrecognized, it must be noted as a serious omission on Brill's part to fail to acquaint his readers with the views of modern or recent authors who have observed cases of typhus fever while possessing all the advantages of the medical progress in differentiating other diseases from them, advantages which were absent in the time of the “great masters of medicine.” The very reactions used by Brill in proving that his symptom-complex is not typhoid fever, namely, the agglutination tests and the blood-cultures, may be named among these advantages.

I was in active practice in western Russia for six years, during which I had the chance to observe three severe epidemics of typhus fever and constantly saw sporadic cases of the disease. Of course, as the etiological factor as well as the special pathology of typhus fever has not yet been discovered, it can be diagnosticated only by the clinical course, and the more I read Brill's description, the oftener I listen to discussions of the theme, the more inclined I become to identify “Brill's disease” with typhus fever. The fairly sudden onset of the affection, the fever curve, the duration of the illness, its termination, the nature of the eruption, the time of its occurrence, the intense headache, the relatively frequent occurrence of herpes labialis, the rapid convalescence, the occurrence of the disease in patients who have previously had typhoid fever, the frequent enlargement of the spleen, the complications involving the respiratory tract, all these I have seen in authentic cases of typhus fever occurring during epidemics and independently of them.

On several occasions Brill has emphasized the intense headache which dominated the clinical picture from onset to convalescence. Other observers dealing with typhus fever have laid stress on this point. Dillingham<sup>2</sup> states that among 560 cases of typhus, intense headache was the most constant symptom. It was either frontal, temporal or diffuse

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<sup>2</sup> Dillingham, T. H. *Diagnosis of Typhus Fever*, New York Polyclin, 1893, p. 97



over the entire head. In a sporadic case described by Cook<sup>3</sup> there was violent headache during the entire period of illness, the pain being characterized by the patient as "awful." To me this is one of the most striking features of typhus fever as I have observed it. I remember especially well an epidemic of typhus fever which was accompanied by an epidemic of small-pox. In the beginning of the disease, before the eruption, the mental diagnosis ran frequently thus: severe facial pain — small-pox, severe headache — typhus fever.

In regard to the skin eruption, I have seen cases of the maculopapular type but likewise other cases showing a roseola and petechiæ, or petechiæ alone or roseola alone. In the first communication, based on seventeen cases Brill<sup>4</sup> described the eruption as a roseola. In his later communication, however, he states that at the time he committed a mistake, the eruption being maculopapular in all cases. In my opinion this retraction is not necessary, I have seen many cases of typhus fever with a roseolar eruption only, coinciding with Brill's early cases except that in two patients the eruption involved the face as well as the trunk and extremities. It should be mentioned that there are rare typhus fever cases which show no eruption at all, the diagnosis being possible only during epidemics. Biernacki<sup>5</sup> has described such cases and I have likewise seen them. Many of Dillingham's<sup>6</sup> cases had a maculopapular eruption, and the description of the eruptions observed by Clark<sup>6</sup> in forty cases which occurred on Blackwell's Island show many that resemble Brill's cases and those observed by me.

The affection of the respiratory tract was striking even in cases of medium gravity: conjunctivitis, coryza, bronchitis were of frequent occurrence, and these manifestations in children when the eruption was macular caused great difficulty in differentiating typhus fever from measles. In grave cases stupor was a marked feature among adults, so that catheterization, for instance, was frequently necessary even in early days of the disease, otherwise the nervous manifestations observed by me corresponded entirely with those mentioned by Brill. I have also seen cases during epidemics which showed fever and an exanthem only without any manifestations from the nervous system.

In my light and medium cases the disease lasted from ten to fifteen days, in a few cases not over a week and very rarely five days, in grave cases up to twenty-one days. The termination was usually marked by an

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3 Cook, A. H. A Case of Sporadic Typhus, *Lancet*, London, 1884, p. 676.

4 Brill, A. Disease Clinically Resembling Typhoid Fever but Without the Vidal Reaction, *New York Med. Jour.*, 1898, p. 48.

5 Biernacki, E. Typhus Exanthic sine Exanthemat, *Gaz. lek. Waiszawa*, 1894, p. 562.

6 Clark, L. Some Observations on an Epidemic of Typhus Fever, *Am. Med. Surg. Bull.*, 1894, p. 647.

incomplete crisis or by a rapid lysis. If no complications occurred, patients could sit up in bed at the end of the fever and leave the bed a few days later. Thus, convalescence was usually rapid. Among complications were observed severe bronchitis, bronchopneumonia, pulmonary gangrene twice, pleurisy with effusion twice, rarely true nephritis, though febrile albuminuria was frequent. In a few cases which ran a fatal course diphtheritic sore throat appeared, usually in the beginning of the second week. Intestinal complications such as frequently occur in typhoid fever have not come under my observation. On several occasions considerable meteorism was present. In nearly all there was obstinate constipation, but in summer diarrhea was often present. Bill states that typhus fever does not occur in summer, but this statement is only partially correct, whenever there was an epidemic in winter, sporadic cases occurred in the following summer. One of the epidemics in which I was actively engaged commenced in February and lasted till August. The Berlin<sup>7</sup> epidemic of 1868 was not arrested until the end of July. It is usually assumed that patients are made immune by one attack of typhus fever, but I have certainly seen a repetition of the affection in the same individuals. In one case the first attack was mild, the second severe. In another instance the disease ran a medium course in both attacks.

I will now proceed to a consideration of the epidemiology of typhus fever, it being my object to present but a few features of the cases I have seen. Were I to present complete descriptions of my medium and light cases, it would amount simply to a repetition of Bill's elaborate communication.

Let us first approach the question whether typhus occurs only in epidemics, and the answer is by no means. Typhus is endemic in many districts of Russia, so that sporadic cases are of constant occurrence there. In many other districts where hygienic conditions are very favorable, typhus fever is but little known, and if sporadic cases do occur, they are of a mild character. As examples of such localities may be mentioned the Baltic provinces of Russia and Finland. When sporadic cases running a mild course, and consequently not accompanied by any mortality, occur in large cities they are usually not recognized. These cases are generally designated as an "uncertain kind of typhus," in other words, "a disease of unknown origin." If one has observed typhus cases in the neighboring small towns, the conviction is soon forced on him that the sporadic cases in the large cities have been of the same character. Small towns are, in my opinion, in a more favorable position for the study of the various types of typhus, one of the reasons being that the entire clinical material passes through the hands of but one physician, as frequently is the case in Russia.

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<sup>7</sup> Obermeier, O. Die ersten Falle und der Character der berliner Fleck-typhus Epidemie von 1868, Berl klin Wchnschr, 1873, p 349

Typhus is endemic not only in Russia, but also in many other countries. Virehow<sup>8</sup> assumed that the endemic typhus of the Slav countries led to the epidemic outbreak in Berlin in 1867-68. Why endemic diseases do not lead to epidemics every day cannot be decided. However, according to Virehow, a special predisposition in the locality and, perhaps, the cooperation of accidental conditions may be responsible. According to Murchison,<sup>9</sup> many epidemics originate from local contagion which may have been preserved in an endemic way, or may have appeared because of hunger and dirt among the inhabitants.

The last epidemic in Breslau, according to Leonhardt,<sup>10</sup> came to an end in July, 1879. In the following years sporadic cases of typhus fever occurred, which in 1883 increased to thirty-six. In 1885-86 not a single case occurred, in 1887 and 1888 two cases each, and in 1892 one case.

In Edinburgh,<sup>11</sup> in the old town, typhus was practically endemic at one time. There was not a single year from 1880 to 1893 without typhus cases.

Vacher,<sup>12</sup> speaking of typhus epidemics in Ireland, said that the affection was not recognized for months, as the physicians did not know anything about the disease. According to him, defective medical education is responsible for this state of affairs, and no time should be lost to remedy it. Typhus, he says further, is not rare, and in large urban centers, where the medical schools are situated, sufficient cases for clinical instruction can be found if looked for.

In Italy and Bohemia the affection is likewise said to be endemic.

Occasionally in the literature there are reports of sporadic cases of typhus. In 1897, four cases were reported from San Francisco by Shanon.<sup>13</sup> In two of these cases the diagnosis was rejected by the local board of health, which subsequently designated them as typhoid. The competency of the physician who reported the cases could not be doubted, as he had had considerable experience with this disease in Central America. Massie,<sup>14</sup> a country physician, reported a sporadic case, adding that a second case had not occurred in the district. In 1897 a few cases of typhus were reported in London,<sup>15</sup> and in a few suburbs of the city.

8 Virehow. Quoted by Obermeier (Note 7)

9 Murchison. Quoted by Obermeier (Note 7)

10 Leonhardt, M. Ueber das Vorkommen von Flecktyphus und Recurrens in Breslau, *Ztschr f Hyg u Infektionskrankh*, 1897, p 22

11 Littlejohn and Ker. The Outbreak of Typhus Fever in Edinburgh, *Brit Med Jour*, 1898, p 1704

12 Vacher, T. Typhus and Its Notification (The Lesson of an Epidemic) *Pub Health*, London, 1890-91, p 263

13 Shanon, N V. *Occidental Med Times*, Sacramento, 1897, p 651

14 Massie, T. A Case of Typhus Fever, *Brit Med Jour*, 1898, p 1134

15 Dudfield, T O. Typhus Fever in London, *Brit Med Jour*, 1898, p 967, *Lancet*, Lond, 1898, p 1016

there were even small epidemics. De Arellano<sup>16</sup> states that typhus fever is not endemic in the capital of Mexico, but is always present in a very extensive zone in the republic. From 1869 to 1891, not a month passed but cases of typhus occurred in Mexico, although epidemics in that interval have been reported only from 1873 to 1877.

These facts show that in many parts of the world typhus is endemic. The epidemic in Edinburgh, in 1899, proved that after eighteen years of immunity an epidemic can occur. From this the conclusion may be drawn that in a community typhus may be present for a long time without leading to an epidemic.

The history of typhus epidemics in New York proves that the disease occurred epidemically only after certain fairly definite intervals.

The first considerable epidemic in New York was in 1847, following the Irish famine of the same year, in 1861 the disease was again introduced by Irish immigrants, and did not finally disappear until three years had elapsed. Since that time it has been twice mildly epidemic in the city, in 1881 and again in February, 1892. In all these instances the fever was brought to this country from regions where it is endemic. In the opinion of Branan and Cheesman<sup>17</sup> typhus had never become endemic in New York, but has always disappeared when suitable hygienic measures were instituted.

Janes<sup>18</sup> asks how it is that the outbreak of typhus occurred in New York in 1881, after an absence of the disease for about fifteen years. It was believed by some at the time that it was brought by tramps from a city in a neighboring state where a number of cases had previously occurred, and this explanation seemed reasonable, although it was never shown to have been the case. He believes that in all probability the first case was a mild, unrecognized one, and was probably followed by others equally mild. This state of affairs, according to Janes, must have extended over a considerable period, until a resident physician in Riverside Hospital suspected typhus fever in one case. His diagnosis was confirmed by Dr. E. G. Janeway, at that time health commissioner. After the announcement of this case the epidemic became evident. Thus we see that Janes, eleven years previously, was not so optimistic as Branan and Cheesman. He believed that in New York typhus might be an endemic disease.

Brill's observations commenced in 1896, but one year before that, Hubbard,<sup>19</sup> of the Riverside Hospital, New York, reported "cases simu-

16 de Arellano, N. R. *Etiology and Prophylaxis of Exanthematic Typhus*, Am. Pub. Health Assn., Concord, 1893, p. 81.

17 Branan and Cheesman. *A Study of Typhus Fever, Clinical, Pathological and Bacteriological*, Med. Rec., 1892, p. 713.

18 Janes, E. H. *Typhus Fever in New York City*, Am. Pub. Health Assn., 1884, p. 301.

19 Hubbard, S. D. *Cases Simulating Typhus Fever*, Med. Rec., 1895, p. 21.

lating typhus" Why this author thought that his cases only simulated typhus and were not the real disease is unintelligible to me after having thoroughly studied his communication

As an important reason for regarding the disease as "of unknown origin," that is, a clinical entity and not as typhus, Brill mentions the absence of fatal cases at the hospital Since his communication first appeared, however, three fatal cases have been reported

The mortality of typhus epidemics has considerably decreased through improved hygienic conditions and modern sanitation, but, of course, this mortality will always depend on the unknown "genius epidemicus," as is the case in other infectious diseases

The Russian prison typhus still shows considerable mortality, perhaps as high as has been stated by the masters of medicine for the typhus fever in their time *Viach* (1909, p 391) makes the following statement

Typhus in prisons is not an accidental manifestation, these institutions being the birth-place of the disease It is the product of our prison conditions True, the overcrowding of the prisons has not commenced yesterday, but it increases every year Since they have never been empty, and new inmates are constantly arriving, the cells can never be thoroughly cleansed, much less disinfected when a prisoner falls ill The prisoners strive even in the metropolitan prisons, unless they receive monetary help from outside

*Viach* (1909, p 140) reports as follows "A typhus epidemic broke out in a provincial prison, in which 1,317 prisoners have been crowded, although there was hardly room for 300"

Under these conditions a mortality of over 50 per cent may be expected In these prison epidemics, nurses and physicians succumb even at the present time The mortality in hospitals and private houses is, however, not as appalling I have no exact statistical material at hand from my three typhus epidemics, but I may state that the mortality was from 6 to 9 per cent In one of my typhoid epidemics I have had a larger mortality (10 per cent) than in the epidemics of typhus fever This, of course, is easily explained by the fact that dietetic rules cannot be carried out as carefully in private practice among the poor, as in hospitals Rigorous diet is not of such great importance in typhus as in typhoid fever, because in the latter intestinal perforation and hemorrhages from the bowels are to be apprehended, which is not the case in the other disease

In eastern Prussia<sup>20</sup> the mortality amounted to 10.25 per cent in the years 1868-69 Tcherepin<sup>21</sup> reported on the typhus epidemic in St Petersburg during 1902 and 1903, as follows "In a period of seven

20 Seliger Die Flecktyphusepidemien in der städtischen Krankenanstalt, z Königsberg, 1 Pt., Beil Klin Wehnschr 1888, p 1028

21 Tcherepin, S Die charakteristischen Eigenthümlichkeiten der Flecktyphusepidemien in Petersburg im Jahre 1902-3, St Petersburg med Wehnschr, 1904, p 52

months 428 patients were treated in the hospital barracks. The majority of the patients belonged to the indigent classes, the mortality was 8.6 and 9.5 per cent, respectively."

In my sporadic cases there was rarely a death, as the majority ran a mild or medium course.

Dillingham<sup>2</sup> gives a description of "so-called typical cases" of typhus, in which recovery took place, and if they are carefully analyzed and compared with Brill's cases, the identity will be apparent. From Littlejohn's<sup>11</sup> statistics of endemic cases in Edinburgh it will be seen that from 1880 to 1889 the mortality was 28 per cent, from 1889 to 1898 only 14 per cent.

In less than ten years the mortality in Edinburgh was reduced by one-half. The mortality in my three typhus epidemics was small, possibly because most of my patients were Hebrews. My observations have shown that Hebrews are usually attacked by mild and medium forms of the disease and that the mortality among them is relatively lower than in other races. As most of Brill's patients were Russian Jews, the mild course and the low mortality may perhaps be explained from this fact. Of other races, a low mortality has been reported by Conseil<sup>22</sup> among Arabs. During the typhus epidemic in Tunis, in 1906, there was a mortality of only 5.4 per cent, and the affection showed a relatively mild course among the Arabs. For this reason the diagnosis of sporadic cases among them was difficult. Gourrier,<sup>23</sup> in 1903, did not have a single death in nine typhus cases among the Arabs. This opinion of the mild course of typhus fever among the Arabs is also shared by Franco.<sup>24</sup> These facts are perhaps of importance in Brill's cases, because his patients belonged to a race in which the course of the affection is much milder even during epidemics.

The most important argument which Brill presents is that the disease is not communicable, and up to a short time ago it was very difficult to discuss this argument. He writes:

One of the nurses in training school, who, in December 1896, went through a severe typhoid infection, was attacked six months later with this disease, though at that time there was no other case of this disease in the hospital or training school. She was the only person I have seen developing the disease within the hospital.

Contagiousness, however, is a relative term. Such factors as unfavorable hygienic conditions and individual predisposition play an important rôle. It may surely be assumed that the contagious substance remains in the hospital and that many patients were not affected simply because they were not predisposed to the affection. This nurse had had typhoid fever

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22 Conseil. *Le typhus exanthématisé en Tunisie, 1906*, Thèse de Paris, 1907.

23 Gourrier. Quoted from Conseil.

24 Franco, F. *Thèse de Paris, 1903-1904*.

six months previously, and this may have been the determining factor I have observed many cases of typhus fever in patients who had had typhoid in the same year. A house physician of the Mount Sinai Hospital told me that the hospital possessed the history of two members of the same family who had become infected with Brill's disease. Warren Coleman observed the affection in four members of the same family in Bellevue Hospital.<sup>1</sup> Dr Lewis A. Conner told me of three sisters in the New York Hospital who almost simultaneously contracted the disease. But even all these cases do not demonstrate direct contagiousness. I do not think that contagiousness, except in the presence of unfavorable conditions or of predisposition, or both, has ever been positively demonstrated. There is to my knowledge in the entire literature only one case (this, however, is very instructive) of typhus fever transferred by inoculation from one individual to another, the author, Motschutkowski,<sup>25</sup> having made the following experiment on himself. From a patient suffering from typhus he obtained a little blood through a small skin incision, he inoculated himself with this and eighteen days later developed a typical typhus fever which took a similar course to that in his patient. Since this author had treated many typhus patients for four years without being affected, he concluded that typhus can be inoculated and that the infectious agent must be in the blood. I mention this case believing that it is singular in the literature.

There is hardly an infectious disease, the spreading of which depends so much on the hygienic conditions as is the case in typhus fever. Well-to-do people, or individuals who can afford the comforts of life, are not greatly subject to the infection. The disease, however, easily spreads in the dwellings of the poor and in lodging houses where there is bad air and little light.

Brill's cases were observed in the wards, not in the private pavilions of the hospital. Consequently, his cases came from the poorer classes, that is, from New York tenement houses. In buildings of this description several inmates are usually affected by the disease during epidemics,

Palatial residences, which are not secure from typhoid fever, scarlet fever and measles, are nearly always immune to typhus. In fact, during epidemics I have very rarely seen typhus among the better class of patients, and if in rare cases it did occur usually no other member of the family became infected, although no precautions in the way of isolation were taken. Whoever is acquainted with these facts will not be surprised that in the well-ventilated wards of the Mount Sinai Hospital, and other equally well-equipped hospitals of New York, nurses, physicians and other patients have not been infected.

In my town, in a small, well-equipped hospital, where during epidemic years there were many patients with typhus fever, as well as a few in

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<sup>25</sup> Motschutkowski Ueber die Ueberimpfung des Flecktyphus, St. Petersburg med. Wehnschr., 1900, p. 30

other years, I never observed infection of nurses or patients. I, myself, have been infected with typhoid and Asiatic cholera, but never with typhus, notwithstanding the fact that I came in close contact with patients during three epidemics.

Strumpell<sup>26</sup> says "In the well-ventilated barracks of the Leipzig Hospital cases of infection with typhus fever of physicians, nurses or patients have only been isolated."

Yet Strumpell speaks of epidemics, Brill of sporadic cases of "acute infectious disease." Wyckoff,<sup>27</sup> referring to the epidemic of typhus fever in New York in 1892, reports "that the medical and inspecting staffs were spared." Of the nurses and sanitary police three or four only have contracted the fever and no one died.

According to Littlejohn,<sup>11</sup> during an outbreak of typhus fever in Edinburgh, seventy-eight cases were treated at the hospital in a few months. Not one of the staff who came into contact with the disease caught the fever. Statistics prove that typhus is not more common amid the dwellers of the houses in the vicinity of the Juarez Hospital in Mexico, than among those who dwell in other quarters of the city. According to Arellano,<sup>18</sup> at the said hospital, where there are always a great number of typhus cases, the disease does not spread among the patients who are in other wards of the same establishment.

Want of cleanliness, insufficient food or food of bad quality, fatigue and moral depression are, according to Brena, predisposing factors in the spread of typhus.

The disease has undoubtedly lost its virulence on account of good hygienic conditions and thorough modern sanitation. It is no longer to any extent a disease of important centers of population served by efficient sanitary staffs.

It now scarcely ever attacks the well-to-do who live in good houses. The fear of its assuming a wide-spread epidemic character no longer exists. It cannot at the present time even be called a prominent danger to armies in the field, or to beleaguered towns. But the disease still exists.

The diagnosis of typhus, according to Mahon,<sup>29</sup> is seldom made, or made only when the disease has become more or less epidemic. The name "influenza" covers a multitude of diseases.

26 Strumpel, A. *Specielle Pathologie und Therapie der inneren Krankheiten*, 1889, 1, 43.

27 Wyckoff, R. M. *The Recent Incursion of Typhus Fever at New York*, Maryland Med Jour, 1891 92, p 463.

28 Brena, T. *Rough Notes on the Etiology of Typhus Fever*, Am Pub Health Assn, 1898, p 206.

29 Mahon, R. B. *The Causes and Management of Outbreaks of Typhus Fever in Rural Districts*, Jour State Med, 1899, p 394.



Before Matignon<sup>30</sup> came to Peking, there was no typhus fever but a *fièvre de Peking* which this author recognized as the European typhus fever. The predominating symptom in these cases was again intense headache.

How mild some of these cases may be is shown by a case of another author,<sup>31</sup> who writes

There are even ambulatory cases, in spite of high fever, prostration and cephalalgia, the patient can walk. A Chinese, sick for five days, with a temperature of 40.4 C (104.7 F) came on foot from a distance to the French legation to ask for a consultation and was able to walk to the hospital, a distance of about 2.5 kilometers, or about a mile and a half.

From this case it may be seen how difficult it may be under certain circumstances to make a correct diagnosis in sporadic cases.

I now come to the discussion of the Manchurian type of typhus.

S. S. Botkin observed in the Far East a peculiar typhus with eruption but without mortality or contagiousness. The pathological anatomy could not be studied, because there was no mortality. When the author read a paper describing his investigations, he found that the affection was known to the local physicians, who called it Manchurian typhus. During a discussion before a St. Petersburg medical society, a physician, Dr. Popoff, stated that he had likewise seen such cases in Warsaw, Poland.

S. S. Simnitzky<sup>32</sup> reported two house epidemics of Manchurian typhus fever in 1907 and in 1908. In both instances the lodging-house and prison of Harbin were visited by the disease. The first time five persons were affected, the second time nine. According to this author, the disease has only slight tendency to spread and caused but slight mortality.

B. A. Barikin<sup>33</sup> states in regard to the "so-called Manchurian typhus," that during epidemics of typhoid and paratyphoid there are occasionally cases which in Europe are regarded as typhus, but they are distinguished by slight mortality and slight contagiousness.

Horiuchi<sup>34</sup> succeeded in cultivating from the feces, and in a few cases also from the urine of patients, a well-characterized bacillus which, from its agglutination with the serum of the patient or of others affected with the disease, seemed to him to be the specific pathogenic factor of this affection.

30 Matignon, J. J. *Le typhus des Européens à Pékin*, *Journal de médecine de Bordeaux*, 1896, p. 437.

31 Matignon, M. *Le typhus à Pékin*, *Archiv de médecine et Pharmacie*, 1897, p. 12.

32 Simnitzky, S. S. *Russki Vrach*, 1907, No. 49.

33 Barikin, B. A. *Russki Vrach*, 1909, No. 2, p. 46.

34 Horiuchi, T. *Ueber einen neuen Bacillus als Erreger eines exanthematischen Fiebers in der Mandschurei während des japanisch-russischen Krieges*, *Centralblatt für Bakteriologie*, 1911, 586.

Ricketts and Wilder<sup>35</sup> quote and publish the most recent observations of the contagiousness and transmissibility of typhus fever and of related infections. According to them, Nicolle and his associates have shown that typhus could be transmitted to the chimpanzee by the injection of the blood of human patients and then the disease could be transferred from the chimpanzee to the macacus monkey. In the latter species it could be propagated by the ordinary body lice.

Spotted fever is a disease which, to judge by the descriptions, has a great deal in common with typhus fever. This disease has been specially studied by Ricketts and Wilder, who have shown that it is not contagious at all, being transmitted by the bites of certain species of ticks, so that the presence or absence of this variety of insect determines the state of the disease in any locality. So far as Mexican typhus, or tabardillo, is concerned, these authors are of the opinion that lice are probably the means of transmission of the disease. The flea is excluded from serious consideration because the season of the greatest prevalence of this insect does not coincide with the prevalence of typhus, while individual cases observed by them seem to absolve the bedbug from all blame in the matter.

The words of these authors<sup>36</sup> in reference to typhus fever deserve to be quoted literally, as they are very much in accord with the views defended in this paper.

It is a peculiar fact that the conception of contagiousness has adhered to typhus up to, and including, the present time. Yet, in view of the facts that typhus, when endemic in the city, remains rather strictly segregated in the poor quarters, and that more or less intimate contact is required for transmission, it is manifest that contagiousness, if present at all, must be of peculiar character and of low grade. Typhus has never overwhelmed a whole city as small pox did again and again in former times. In recent years, however, belief in the theory of insect transmission of typhus has extended widely, as affording a better explanation of the epidemiological features of the disease.

If Nicolle's results in transmitting typhus by means of lice be provisionally accepted, they throw additional light on the apparent immunity of Brill's ward patients to the infection from neighbors suffering with the disease he has described. It is well known that lice rarely travel from bed to bed as fleas and bedbugs do, more intimate contact than mere proximity is required for their migration and, with it, for the transmission of any infection they may carry. It may be accepted that the wards of the Mount Sinai Hospital show no exceptions to these observations.

I cannot enter here on the details of the clinical picture, but from descriptions the Manchurian type of typhus seems quite similar to Brill's and to the mild and medium cases which I have seen in European Russia.

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35 Ricketts and Wilder. The Typhus Fever of Mexico (Tabardillo), *Jour Am Med Assn*, 1910, iv, 463.

36 Ricketts and Wilder. The Relation of Typhus Fever (Tabardillo) to Rocky Mountain Spotted Fever, *THE ARCHIVES INT MED*, 1910, v, 361.

The various observations, both personal and taken from recent medical literature gathered in this paper, show that the symptom-complex described by Brill is identical with that of the mild and moderately severe cases of typhus fever. In other words, his cases are not a new "clinical entity" but examples of an old though nowadays but imperfectly known disease. Typhus contagium, too, may always exist in a community yet not necessarily lead to an epidemic at any definite time, for innumerable local conditions may be the determining factors in the development of an epidemic. Who knows but that the cases "simulating typhus" and reported by Hubbard and Brill are not direct descendants from the cases of the epidemic of 1892?

In any case, mere diminution of mortality and contagiousness should not lead us astray, for it is impossible to estimate the effect of modern hygienic and sanitary precautions on the character of such a disease of filth, hunger and poverty as typhus fever. Moreover, fatal cases have been observed by Brill in patients treated under the best conditions, that is, in the hospitals, and the mortality of from 6 to 9 per cent observed by me in the general practice in a small Russian town does not then appear so greatly different. The fact that mostly Hebrews were affected among Brill's cases must also be remembered, the statistics I have mentioned in discussing typhus among the Arabs shows how important are the racial peculiarities in this connection.

Of course, time alone will decide the question of properly classifying the symptom-complex so ably observed and described by Brill. In the meantime, however, it does not seem to me to be part of wisdom to retain his nomenclature of a "disease of unknown origin," but rather call it New York typhus, just as the typhus of Peking and of Manchuria has been named. This would go far in calling the attention of physicians to the clinical picture concerned, and, moreover, not connote something surely rare and unusual. The name "typhus" need cause no panic, as I have tried to show in the preceding pages, for it is no longer equivalent to the terrifying news, *Hannibal ante portas*. Modern conditions have robbed this scourge of mankind of much of its terror.

#### CONCLUSIONS

- 1 Typhus fever occurs sporadically in many regions
- 2 Mortality from typhus fever no longer reaches the high figures quoted by old observers of the disease
- 3 Typhus is little contagious wherever good ventilation, abundance of light and good hygienic conditions exist
- 4 Epidemics of typhus may occur at very infrequent intervals even where the disease is endemic
- 5 Brill's symptom-complex is identical with mild and moderately severe cases of typhus fever

123 East Ninety-Fifth Street

# CORRELATION OF CLINICAL PROGRESS WITH THE RESULTS OF IMMUNOLOGICAL STUDIES IN PULMONARY TUBERCULOSIS \*

ALFRED H. CAULFEILD, M.B.  
GRAVENHURST, CAN.

One of the most striking features of tuberculosis is its clinical variation. Thus, if one is given a picture of the amount and kind of anatomical involvement, one can form but little estimation of the probable duration of the infection, its past variations or future possibilities, and one frequently finds that, if to this there be added the results of the general clinical inspection and as accurate an anamnesis as it is possible to obtain, the careful observation of some weeks is further necessary before one feels acquainted with the type of case, which even yet may develop unexpected traits. Intuitively, one may feel indefinite indications which may or may not be subsequently verified. Of course these statements are comparative, and like all such in medicine depend to some extent on the clinical experience and judgment brought to bear on the case, but under any circumstances these considerations seem to be distinguishing features of this infection.

These peculiarities help complicate both the diagnosis and prognosis and are chiefly concerned with the resistance of the patient. It is on the type of resistance that I wish to present data. Before attempting this, it seems necessary to consider also the unusual range of tuberculous infections. Roughly, we have the clinically normal case which gives tuberculin reactions, involvement of glands, serous membranes, skin, etc., which apparently remain confined to these structures, the variations of pulmonary tuberculosis, and finally the typical miliary tuberculosis or tuberculous septicemia.

Now the various immunological procedures that have been meant to aid diagnostic or prognostic values even in pulmonary tuberculosis have been confined to certain distinct types, but in the main, it has been the results obtained with the "normal" that have prevented the general acceptance of the tests in purely clinical work. Usually the tests fail to give 100 per cent positive results with cases, and they involve the normal as well, so that the general verdict is "Of what use are they in doubtful cases in which they are most needed?" It is probably not the procedures that are at fault, but rather our method of application.

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\*From the Pathological Department of the National Sanitarium Association

Agglutination, the precipitin and tuberculin reactions, leukocyte and opsonic estimations share this disadvantage

It however, one uses these methods not as an aid to diagnosis or prognosis at first, but rather to demonstrate evidences of the biological state — as one would use the various methods of a physical examination of the chest to depict the anatomical involvement — the results assume not only an interesting but a valuable force. Obviously, the biological state, if demonstrated and understood in its entirety, must precede rather than accompany the anatomical involvement. The clinical responses are due to the biological variations.

As a means of showing these biological variations I shall present certain procedures,<sup>1</sup> which will frequently be referred to for greater detail, all of which have been carried out on fairly large numbers of cases, and further attempt to correlate the results of these with certain clinical recognitions.

### I TUBERCULIN REACTION

1 A positive result means only that the subject has been exposed to tuberculous infection and has reacted biologically. This specific state lasts for a varying period in both clinically normal and tuberculous subjects. Certain cases of pulmonary tuberculosis after years of infection may still show this markedly. This state may be taken as evidence of one part of the mechanism of resistance, and by itself can demonstrate only approximately the presence or absence of those bodies concerned in its production.

2 A negative result presents three considerations

A No exposure

B Loss of sensitiveness

C Anergy — the development of a condition refractory to tuberculin (comparable to the antianaphylactic condition in anaphylaxis)

It is not always possible to distinguish, in cases giving slight reactions, between the second and third types. When loss of sensitiveness is taking place, it represents a partial victory by the infection against the host, and the accompanying clinical correlation probably depends on the extent to which the particular patient is utilizing the bodies concerned in the reaction for maintenance of life. This can sometimes be approximately gauged by the estimation of other resistance products. The refractory condition does not seem to represent an infection victory but rather the reverse. It is not only convenient to take this tentative hypothesis, but apparently true clinically.

### II COMPLEMENT DEVIATION

Complement deviation must be considered in both a specific and non-specific light. As the former it is the true Bordet-Gengou phenomenon,

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<sup>1</sup> These have been published in the Jour. Med. Research, LVIV, No. 1

as the latter it is exemplified by the Wassermann reaction for syphilis. Probably the results obtained in tuberculosis are influenced by both factors, but accepting a certain type<sup>2</sup> of positive reaction as evidence of tuberculous sensitizers, the following statements can be made

1 It is not obtained in the clinically normal giving tuberculin reactions

2 Its presence in the tuberculous is usually found among the more unfavorable type

These facts as well as other considerations suggest two theoretical conceptions either tuberculous sensitizers are not produced by favorable cases and "normals" showing tuberculin sensitiveness, or they are produced, though their presence is in some way masked

### III INHIBITIVE REACTION

In attempting to solve this problem it became possible to show with the serums of certain favorable cases not giving evidence of sensitizers, an antigen-serum combination or effect that is non-attractive for complement. Consequently, with the technic of the deviation test complete hemolyses results<sup>3</sup>. This reaction capacity can conveniently be termed inhibitive. For purposes of expression only, it is convenient sometimes to speak of such inhibitive-reacting serums as containing inhibitin. Further, if such antigen-serum mixtures are again treated by a sensitizer serum, the end-result of complete or no hemolyses can be shown to depend on the relative strength of the opposing serums.

### IV INDIFFERENT REACTION<sup>3</sup>

From the technic employed, a third type of serum becomes evident in that there is no evidence of either sensitizers or inhibitin. This can conveniently, for these purposes, be termed "indifferent" (or Class III).

From the results of the immunological procedures so far dealt with, one may tabulate the following demonstrations

1 By tuberculin reaction

A Allergy or marked sensitiveness (host defense)

B Loss of sensitiveness (infection victory)

C Anergy or refractoriness (host defense)

2 By complement deviation and its modification

A Complement fixation — tuberculous sensitizer (Class II)

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2 This has been to some extent discussed (Jour Med Research, see Note 1) and will be dealt with again in a later publication

3 As outlined in the previous paper the inhibitive serum effect becomes differentially demonstrated when employed with strengths of antigen, which of themselves non-specifically fix complement. With true antigenic strength, no more is demonstrated than that these serums do not fix complement. For practically all this work an alcohol ether extract of the bacillus has been used as antigen

B Inhibitive reaction — inhibitin (Class I)

C Indifferent reaction — (Class III)

### 1 *Correlation of Certain Clinical Considerations with Tuberculin Reaction Results*

*A Onset* — Typically this is acute with cases showing marked sensitiveness, a history of which has never been obtained in my comparatively few definite instances of refractoriness

*B Duration and Involvement* — With increase of involvement usually sensitiveness tends to disappear, and as a general rule with length of duration also. There are, however, instances of marked sensitiveness being maintained throughout a long period (three to five years) of infection with extensive involvement. In a few instances, considerable variations of sensitiveness have apparently obtained throughout the course of the infection

*C Variation* — When this is marked and acute with regard both to clinical response and anatomical involvement, it has in my observation been confined to cases showing marked sensitiveness. The reverse also obtains, viz., definitely refractory cases do not show marked or acute clinical variations of response and anatomical involvement

*D General Prognostic Values* — Loss of sensitiveness is likely to be followed by retrogression, as has been outlined already in the theoretical remarks on the tuberculin reaction. Not all cases showing marked sensitiveness or refractoriness, however, can be classed as favorable without further discrimination by the results of the following reactions. It would seem that the results of this additional biological discrimination harmonize with certain opposing observations on the prognostic value of the different tuberculin reactions

### 2 *Correlation of Certain Clinical Considerations with the Reaction of Irritation (Tuberculous Sensitizers)*

*A General Tendency* — Usually they are cases of doubtful tendency and extremely liable to acute and sudden clinical outbreaks with often corresponding alterations in the anatomical involvement. As far as can be judged, all show tuberculin sensitiveness, usually this is marked

*B Temperature* — This is frequently pronounced in the outbreaks. From considerable opportunity for observation where this has not been checked by continued, even absolute, rest in bed and by contrast with reverse treatment, it would seem that in these cases a repeated record of even 99 F° should be checked by rest in bed, and if this is not effectual the rest should be made absolute

*C Variations in Progress*—One case (864<sup>1</sup>) has come under observation in which the fever and retrogression of the case eventually became beyond control, resulting in early death. This patient with considerable irregularity in her fever chart, with frequent records of 100 F and more or less often 101 F and 102 F, alternated at first from periods of some rest in bed to the activity of being up and about. Biological observations were repeatedly made, and latterly as the severity of the clinical response became more marked, it appeared that the sensitizer content increased, with concomitant loss of thermolabile quantities in the serum. This is the only case beginning with slight involvement that has run a rapidly fatal course when these routine biological procedures were performed, but from certain other closely related immunological tests it seems fair to infer that these conditions were present in two other cases with similar histories. This conclusion is strengthened by several incomplete observations such as the following. Case 1761 was referred to the laboratory as an instance of more or less frequent onsets of temperature, had been classed as Turban Stage I in April and on the second subsequent examination in October as Turban Stage II with increased activity. Three tests at different times showed the presence of tuberculous sensitizers.

Since the earlier observations made on cases, many of which have given very distinct indications toward early and fatal terminations, it has become evident that favorable local progress may occur in these cases, but in every instance in which this has occurred, rest has carefully been enforced. In this connection the following case may be reported.

CASE 1052 has shown remarkable power to "clear" (spring 1909) without retraction, the anatomical condition from a Turban Stage III of marked activity of at least a year's duration. About a year later, after a prolonged setback during which time this serum content was present, striking retraction of the chest resulted. The reaction was last obtained early in June, 1910, since then the temperature has gradually subsided and the general well being has gradually improved. Since August, 1910, the charts have shown a practically afebrile condition. At this date, the chest for the first time showed some evidence of fibrosis, although unfortunately it was impossible to carry out the biological tests. Later, in November, the retraction had become marked with improvement in the physical signs, and for the first time there was no evidence of the sensitizer content, although the tuberculin sensitiveness was as marked as at the first estimation. The condition of well being and lack of clinical response at both favorable periods are indistinguishable, the type of local improvement and the serum reactions alone are different.

Two other cases which illustrate variations that have been fully followed are as follows.

CASE 1169—Aug 10, 1910. A man aged 22. General appearance at present not good.

*Weights*—Admission, 158, normal, 170, 145 at 15 years, present 174.

*History*—Diagnosis was made May, 1909, when the patient entered a hospital for bronchitis, he had not felt well for a greater part of the year, particularly in January when he stayed in bed with fever without medical attention. After



diagnosis, the patient, on leaving the hospital, resumed work and felt well till August, at which time he was taken quite suddenly with fever. With more or less rest he improved, began work in October and continued till January, 1910, when a second breakdown occurred. He entered a sanatorium January, 1910, as Turban Stage II, moderately advanced. He was discharged Feb 3, 1911. The institutional charts show variations but no maintained improvement. Apparently, there was an increasing number of slight outbreaks from June till November. From November 7 till December 6 the temperature record shows an irregular curve with several registers over 100 F, during which time the patient might be said to be on more or less rest in bed. From December 7 till January 5 there is no register above or much below 98 F. On January 5 there is a fairly distinct curve reaching 101 F, which acuteness subsided January 16. January 13, absolute rest was enforced.

The following biological data have been obtained

Nov 3, 1910 Class 2 (Tuberculous sensitizers)

Nov 16, 1910 Class 2 (Tuberculous sensitizers)

Jan 3, 1911 Class 3 (indifferent reaction)

Jan 14, 1911 Class 2 (tuberculous sensitizers)

Feb 3, 1911 Class 2 (tuberculous sensitizers)

From the biological work it seems impossible to represent graphically these correlations in their exact quantities—if such do exist—but the accompanying diagram may serve approximately to illustrate

CASE 1371—March 11, 1910, a man aged 19. General appearance fairly good

Weights—Admission 121, at time of investigation, 134, normal (approx), 126

*History*—Diagnosis made Aug 3, 1910. The patient, though not confined, had been under treatment for pleurisy since April, and frequently examined for pulmonary involvement, for about a month previous to diagnosis of pleurisy he had not felt well, having had indefinite chest pains and some shortness of breath.

*Institutional Charts*—September, Turban Stage II, moderately advanced—right sided lesion with very distinct percussion and auscultatory signs. By December 31, the charts are marked clear with the exception of slight signs over the posterior apex and slightly more marked conditions about the front apex of the lower lobe. The laboratory chart of Nov 22, 1910, shows slight involvement on the left side as well, a further anatomical interpretation was made of marked pleural involvement.

*Biological Data*—November 3 Von Pirquet 50 per cent O T (10 cmm) color 30 x 30 mm from second to fourth day with subsequently gradual subsidence, swelling corresponds and is soft in character.

November 3 Class 2, i.e. tuberculous sensitizer serum

December 16 Class 2, tuberculous sensitizer serum

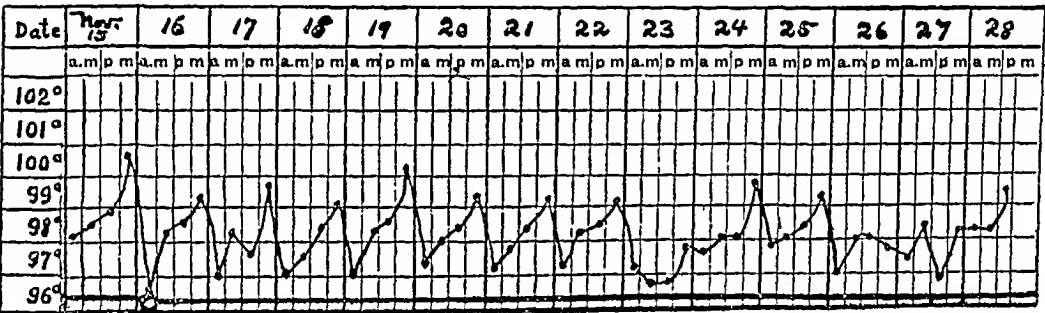
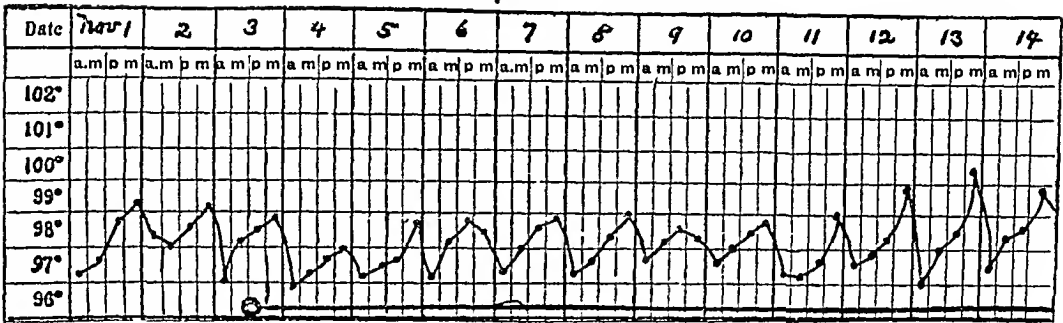
Apparently, steady local as well as general improvement took place in the presence of tuberculous sensitizers.

*Treatment in Particular*—Tuberculin and rest for a temperature of 99 F which has occurred on three occasions.

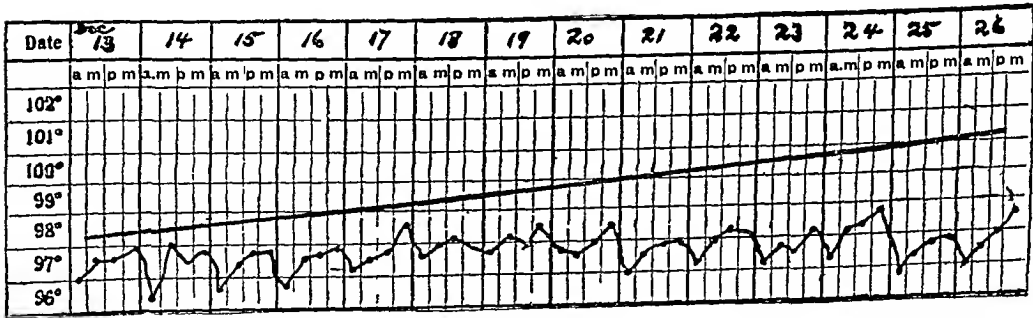
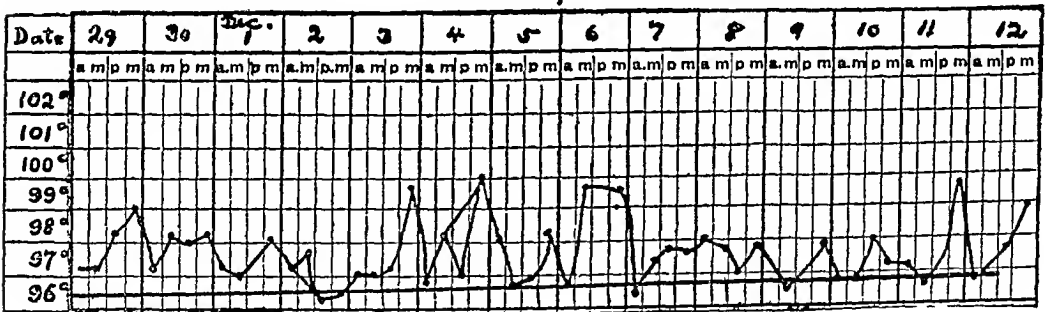
This patient, in contrast to the preceding, made continued progress and the sensitizer content eventually disappeared.

*D General Considerations*—These cases, when persistently showing retrogression, have given with increase of the sensitizer strength a loss of certain thermolabile constituents. If we base our conclusions chiefly on earlier observations, these cases are extremely liable to develop unfavorable progress, unless rest is carefully enforced. With this régime, instances have occurred of stationary and more or less favorable local

a



b



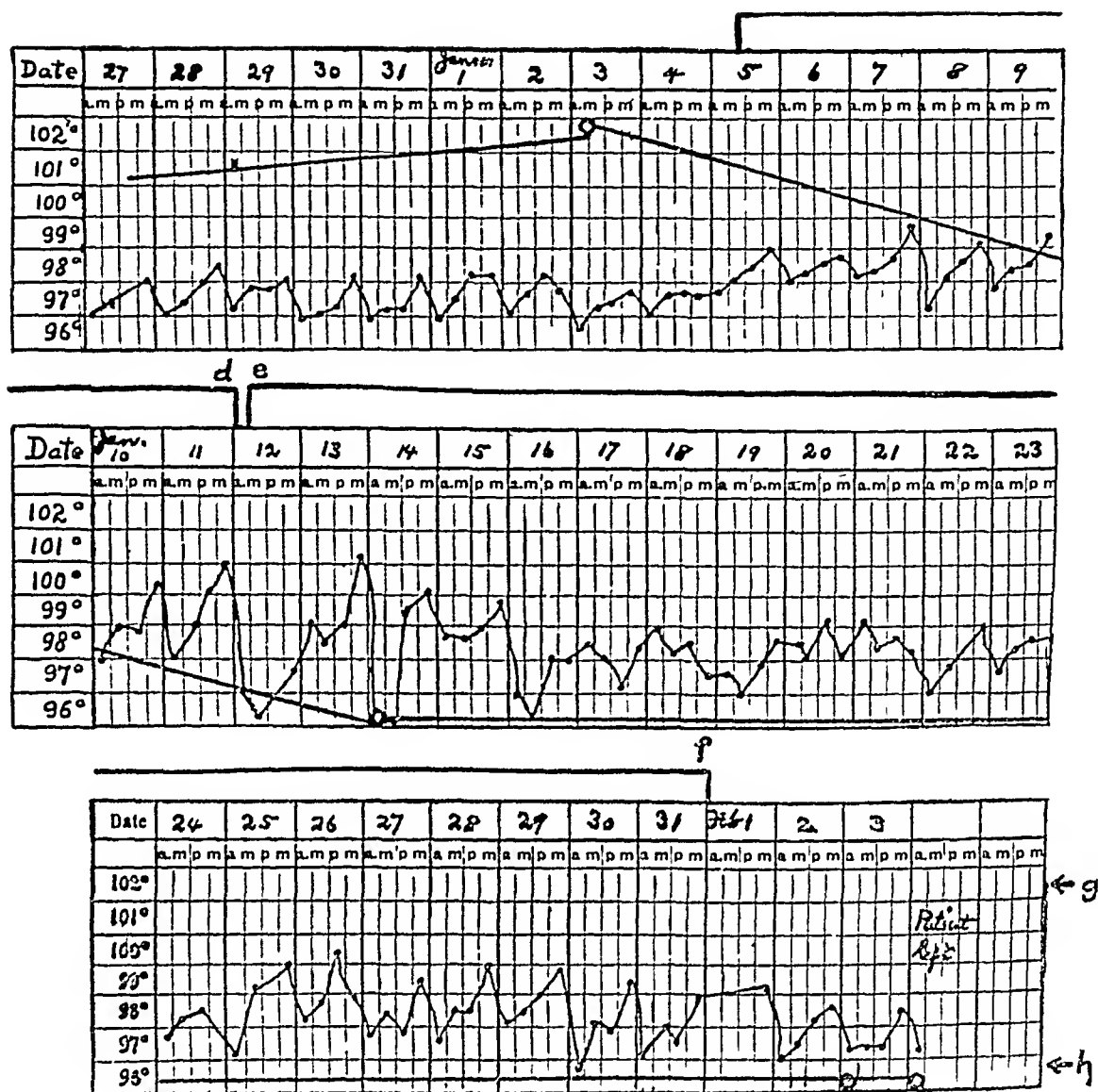


Fig 1—Chart of Case 1160 Line with nodes indicates temperature Heavy straight line indicates serum reaction curve The circle (o) indicates dates of serum reaction From a to b more or less incomplete rest From c to d rest From e to f absolute rest attempted—not quite satisfactorily obtained The mark g indicates indifferent serum reaction, h indicates tuberculous sensitizers

changes, under which circumstances eventually the sensitizer serum content has with temporary exceptions disappeared after, as far as can be judged, the subsidence of the clinical responses

### 3 Correlation of Clinical Considerations with the Inhibitive Reaction

*A Early Cases*—Patients with slight involvement (early cases) in good general condition, nearly, if not always, have given this reaction The possible exception is noted chiefly because of the doubtful nature of the diagnosis in certain cases that might be included in this class

*B Normals*—Clinical normals giving tuberculin reactions have so far all shown some inhibitive reaction, while (few observations made)

favorably progressing cases of glandular and serous membrane involvement have given this in full

*C Involvement*—Quite frequently cases are found with extensive anatomical involvement and signs even of fairly marked activity, in these cases considerable work may show no unfavorable effect. In all these the inhibitive reaction has been present to some extent, though not usually to the full extent.

*D Temperature*—This correlation has been obtained in two somewhat different fashions. In the first method, observations have been made to a considerable extent on about twenty-five patients in bed, but for various reasons these observations have not been systematically repeated. Among these, some have shown traces of the reaction, a few have shown the complete inhibitive reaction, while the immediate progress has proved doubtful or stationary. In every case (with one exception, in which the test was not made) these doubtful subjects have shown distinct loss of tuberculin sensitiveness. The results were almost entirely obtained among various types of Tuihan Stage III involvement, in which the work has shown that varying amounts of inhibition may be obtained with considerable clinical response and a bare ability to maintain a stationary local condition. Theoretically, this does not seem at variance with one's conceptions if the reaction is regarded as a quantitative method, indicating what seems to be the main type of resistance contents. In view of these conditions one feels that each case must be considered by itself in the fullest manner both clinically and biologically. Among these cases with febrile tendencies more than elsewhere, there have seemed to be questions of internal medicine and surgery with their possible bearing on the general welfare of the patient—and also where the involvement is slight, questions of diagnosis. Occasionally, observations have been made regarding the beneficial effect of exercise on certain of these cases hitherto confined, and this is in extreme contrast to my experience with cases showing tuberculous sensitizers. These limitations and indications are somewhat fully exemplified by the following case.

CASE 1109—Aug 31, 1910, a woman, aged 25. General appearance, slight, temperamental, moderately good.

*Weights*—Admission, 117, at time of investigation, 121, normal, 120.

*History*—Diagnosis made August, 1910, the patient sought medical advice because of slight cough and marked lethargy which seemed to increase after an attack of measles in May, the symptoms were indefinitely spread over the preceding year. During the two weeks preceding the investigation, and occasionally before, the patient was in bed because of fever.

*Institutional Charts*—Aug 31, 1910 (first examination classed as Tuihan Stage I) Right apical involvement extending in front to third rib and behind to well below the posterior apex, moderate signs of activity noted. The second examination showed a stationary condition.

Dec 8, 1910 (third examination) No signs of activity are recorded, impairment of resonance being noted only at both anterior and posterior apices.

The fourth chart, Feb 22, 1911, shows but slight signs of doubtful character

*Biological Data*—Nov 6, 1910 V Pirquet 50 per cent O T (10 cmm) maximum color (faint) 30 x 38 mm on fourth day with somewhat more extensive swelling, soft in character

Nov 3, 1910 Class 1—with very slight inhibitive reaction

Nov 16, 1910 Class 1—some inhibitive reaction

Dec 17, 1910 Class 1a—full inhibitive reaction

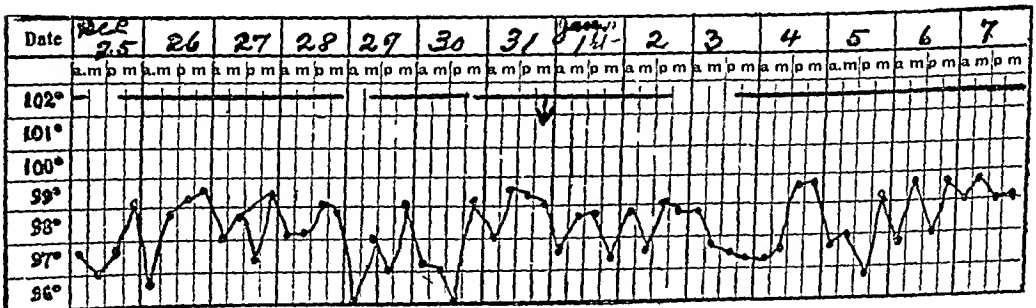
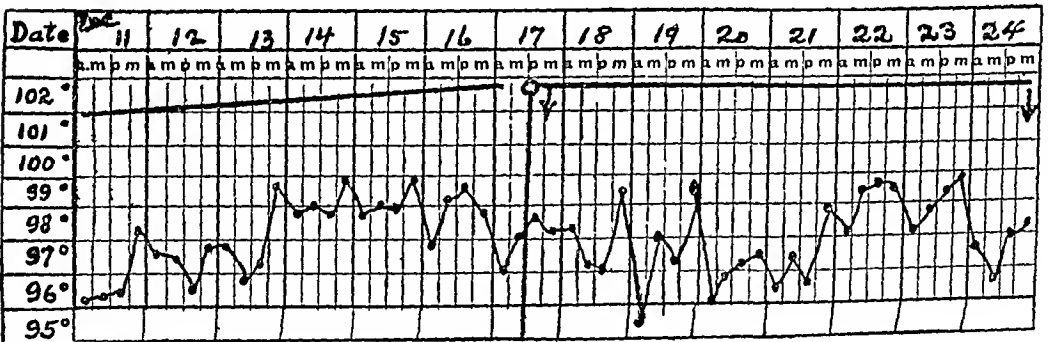
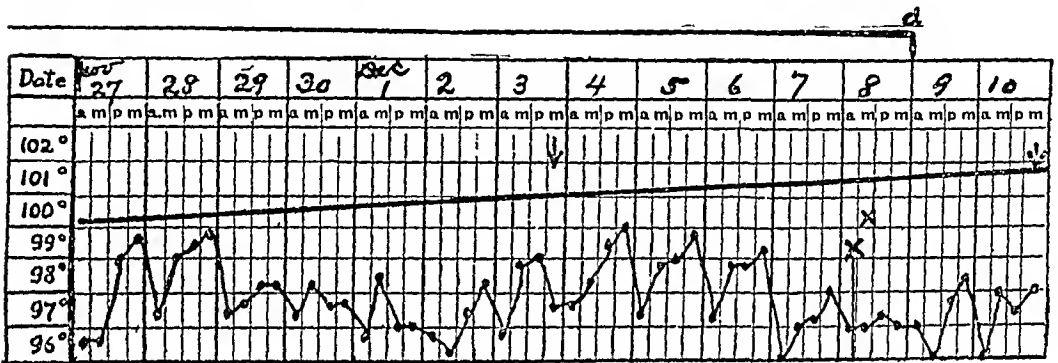
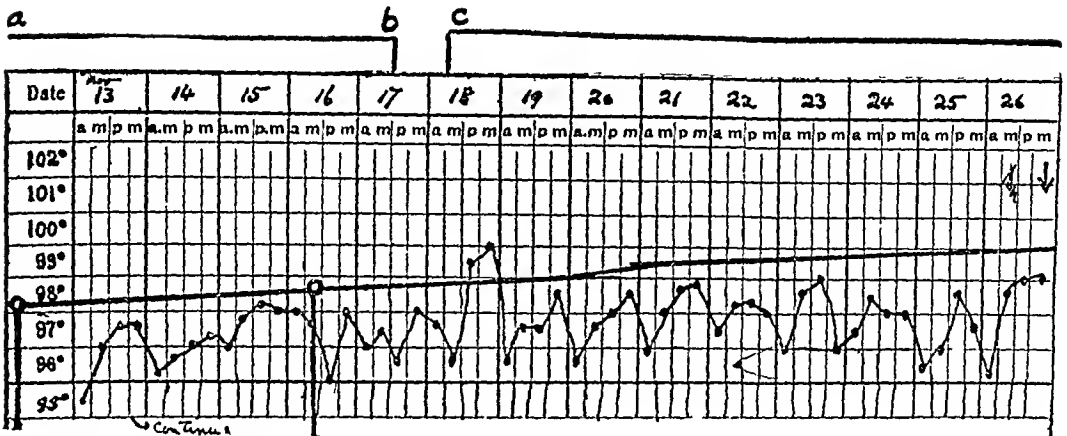
In this instance, the considerations regarding questions of internal medicine have not been definitely settled so that they need not be taken up here, although for evident reasons they have to be considered. Chiefly on account of the biological findings it was requested that this case be kept up in spite of the temperature, and tuberculin was administered. The possibility of the medical complication would not have been considered, had not the biological data been obtained. Beyond the biological evidence the indications pointed toward probable retrogression, until the time of the third examination, all examinations were made by the clinical staff.

The second fashion in which temperature has been observed has been on subjects more or less approximating the type described under Paragraph C of this heading, and in connection with whom for various reasons more systematic checking has been possible. Here, in several instances, after varying periods of temperature (where the inhibitive reaction has remained the same) I have usually been unable to satisfy myself of any definite local change, while later the patients apparently assumed their previous condition of well-being.

*E Variations*—This paragraph can conveniently be introduced by the statement that up till the present there has been no instance of a case giving and maintaining a full inhibitive reaction, marked tuberculin sensitiveness or definite refractoriness that has not progressed very favorably—usually making either an arrest or apparent cure, although this naturally is dependent on the time of observation.

This ability to resolve fairly rapidly the anatomical involvement—as judged by our physical methods—in contrast to those cases in which this does not obtain, although the patient may make slow and slight local improvement or good progress in the general well-being, seems very definitely associated with these two biological conditions. That other biological conditions may sometimes approximate this clinical result is shown in certain of the histories under Heading 2, and as well in certain subjects about whom it is not possible as yet to arrange the scattered immunological data.

Probably owing to the fact that very few patients reach my department until some time after arrival, there have been only a few instances of increase in the inhibitive serum content. In one of these, particularly the accompanying clinical improvement has remained in marked fashion (Case 1107).



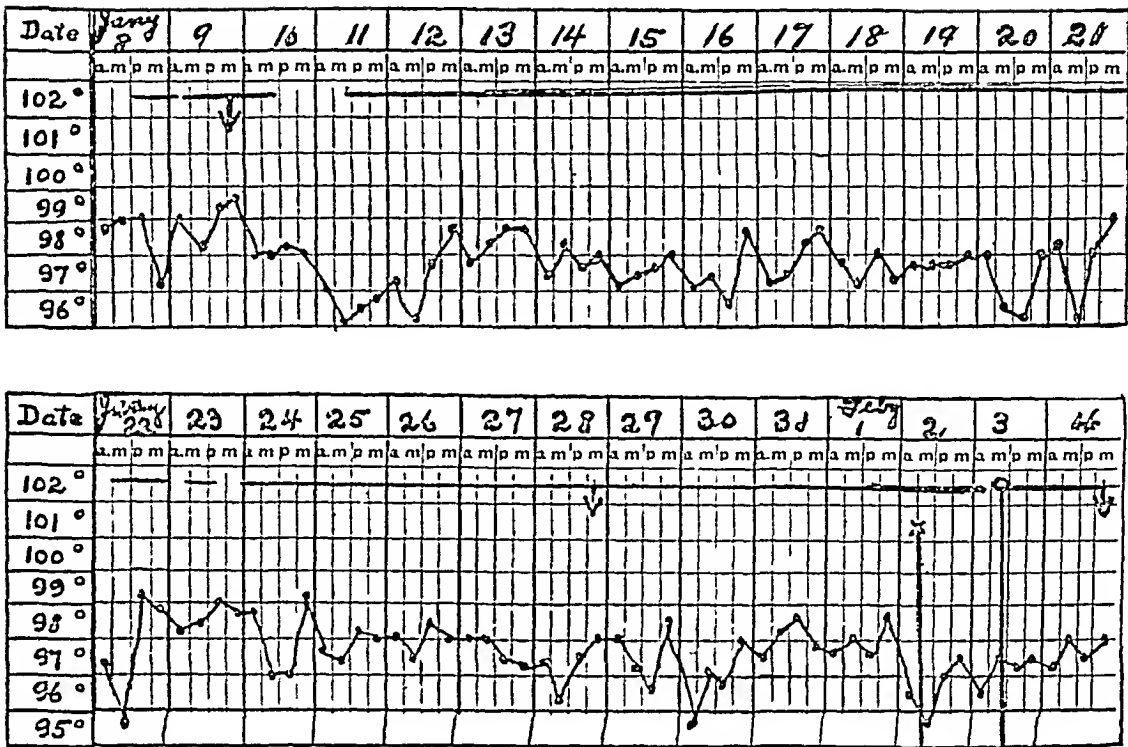


Fig 2—Chart of Case 1109 Line with nodes indicates temperature Heavy line indicates serum reaction curve (when at the top, inhibitive reaction, when at the bottom, indifferent reaction) The circle (o) indicates dates of serum reaction (beginning with third reaction),  $\alpha$  indicates third and fourth physical examinations, respectively Knowledge of anatomical progress remained in *status quo* (Turban Stage I, with activity) until third examination on Dec 8, again in February showing the continued improvement As far as determinable, the rise in the inhibition content preceded the favorable local changes

On the other hand, there have been many instances of loss of the inhibitive reaction followed or accompanied by slight increase of local involvement, or suggestive specific clinical response, or both, when often at the time of the biological observations this might not have otherwise been observed Particularly lately, as the number of patients and the time since their reaction observation increase, have these correlations been accumulating This has been so definite and is of such importance that it seems worth while to outline instances dealing with different amounts of involvement and type

CASE 312—A man, aged 24 General appearance splendid

*History*—Diagnosis made January, 1910, the patient had had a small hemorrhage while playing sport in December, 1909, later the *B tuberculosis* was found in the sputum, there was a history of some lassitude and slight cold during December only

*Institutional Charts*—January, 1910, slight right apical lesion with involvement of the posterior apex (classed Turban Stage I incipient)

By June 16, the charts are marked clear with the exception of very slight evidences at the posterior apex During August and September, the posterior apex is marked clear, although again some slight evidences are marked anteriorly These two charts seem to be the best From this time onward, varia-

tions have increased so that the December and January (1911) charts show an anterior involvement extending slightly into the middle lobe and record showers of râles on coughing

*Biological Data*—Jan 26, 1910 Von Pirquet 50 per cent old tuberculin (10 c mm) maximum color 60 x 50 mm on the third day with indurative swelling 30 x 25 mm, some lymphangitis

June 12, 1910 Class I The full inhibitive reaction had been obtained many times previous to this date, as this serum had been used considerably in advancing the theoretical parts of the work This was the last date, on which this full inhibitive reaction was obtained, although subsequent work on June 14 suggested that it was not so strong or efficient as previously During August work with a new extract which proved unreliable gave certain indications that the reaction was less marked However, the conditions at the time of the last reactions were such that no positive value can now be attached to these indications

Nov 3, 1910 Class 3 (indifferent reaction)

Nov 17, 1910 Class 3 (indifferent reaction with the faintest suggestion of inhibition)

Dec 16, 1910 Class 1a (full inhibitive reaction)



Fig 3—Line with nodes indicates subjective indications, line with circle (o) indicates serum reaction, line with crosses (x) anatomical involvement Chart of Case 312 (a) Top full inhibitive reaction, no evidence of anatomical involvement, subjective indications, normal, (b) middle indifferent reaction (Class III), Turban Stage I, suggestion, (c) bottom tuberculous sensitizers (Class II), Turban Stage II, definite

During the latter part of September and October and part of November, this patient gave rather indefinite symptomatic complaints that might have been explained by a saturation with sanatorium life At this time the patient took a considerable number of leaves of absence During December the general condition improved It should be stated here that the physical charts<sup>4</sup> were made without knowledge of the biological findings until after November 3, and that the charts exhibited their fullest involvement only some time after the biological variations and at a time when these latter had returned to their former favorable condition If the indefinite general symptoms can be accepted, the biological relations accompanied them (unfortunately repeated cutaneous tests were not feasible) and definitely foreshadowed the anatomical involvement as inferred from the physical examination These remarks may be graphically charted in an approximate fashion (Fig 3)

CASE 1372—M, a man, aged 19 General appearance, very good

Weights—Admission, 149, at time of investigation, 155, normal, 146

<sup>4</sup> This remark applies to most, if not all, charts quoted as institutional The observations, clinical histories, etc, have been made by the pathological department It seemed, however, that for this paper the use of the physical charts of the clinical staff would show an unbiased parallel



*History*—Diagnosis made August, 1910, the patient had passed through treatment by three physicians for lethargy and cold with cough since March, these symptoms were particularly noticeable since April, the highest temperature recorded was 99 F Family history marked

*Institutional Charts*—November 5 Turban Stage I incipient, slight left apical involvement to third rib in front and the posterior apex behind

Dec 9, 1910 There is an impression of possibly less involvement

Jan 17, 1911 Bilateral involvement both anteriorly and posteriorly without much evidence, however, of activity, might be classed as Turban Stage II

The results of the laboratory charts made in November and January correspond, though less noticeably, to this variation, further, certain anatomical interpretations made in the first were obscured or altered in the second

*Biological Data*—Nov 16, 1910 Class 1a (full inhibitive reaction)

Jan 14, 1911 Class 3 (indifferent reaction with the faintest suggestion of former Class 1 phenomenon)

Feb 3, 1911 Class 3

The first chart shows variation occurring in January There was nothing in the patient's general condition to suggest that a change of progress was taking place, which is perhaps the fairest fashion to interpret the anatomical findings under the routine circumstances The case has been afebrile and has shown continued improvement in general well-being

CASE 1105—Sept 3, 1910 A man aged 20 General appearance—good, well nourished

*History*—Diagnosis made November, 1909 (after a two weeks' illness of acute onset with temperature of 103 F), the certainty being confirmed by the presence of the *B tuberculosis*, the year previous to diagnosis suggestive but ill-defined symptoms

*Institutional Charts*—December, 1909 Bilateral involvement of moderate activity classed as Turban Stage II, moderately advanced By August the charts showed very distinct improvement From this date till the present, slight variations are shown which practically leave them in *statu quo* in contrast to the previous improvement

*Biological Data*—March 9, 1910 Von Pirquet 50 per cent old tuberculin (10 c mm) color 30 x 20 mm with indurated swelling

March 9, 1910 Conjunctival 5 per cent old tuberculin (10 c mm) + +

April 19, 1910 Class 1a (full inhibitive reaction)

June 12, 1910 Class 1 (partial inhibitive reaction)

Nov 3, 1910 Class 3 (indifferent reaction)

With the inhibitive reaction there was always some deflection of complement with antigenic strengths, a result noticed in later work with serums, which often subsequently lost the reaction content Certain symptomatic evidence corresponds to the lack of improvement, and very definitely is this evident with the temperature records These from March 16 till August 3 show no register beyond 98.4 F From this time on, there are many but irregular variations outside the normal range

CASE 302—Clinical normal April 16, 1910 (Third cutaneous test on left forearm) Von Pirquet 50 per cent O T 10 c mm

April 17 Color 10 by 12 mm—no swelling

April 18 Color 15 by 18 mm—no swelling

April 19 Color 16 by 20 mm with equal swelling that is clear cut and indurative

April 20 Color 18 by 20 mm with equal swelling that is clear cut

April 21 Gradual subsidence

April 16 Conjunctival 5 per cent O T (10 c mm) negative

October 7, 1910 Von Pirquet 50 per cent O T (10 c mm) on right forearm

October 8 Color 20 by 18 mm—no swelling

October 9 Color 20 by 20 mm—no swelling

October 10 Color (patchy) 20 by 20 mm—no swelling

October 11 Gradual subsidence The reaction was not affected by exercise and the color throughout was very easily pressed out

Up till the following data, all clinical normals giving tuberculin reactions had shown repeatedly "some" inhibitive reaction with one doubtful instance

Nov 3, 1910 Class 3 (indifferent reaction)

November 16 Class 3 (very slight evidence of inhibitive reaction)

Jan 3, 1911 Class 1a (full inhibitive reaction)

February 3 Class 1a (full inhibitive reaction)

This is the only example found of a clinical normal giving a full inhibitive reaction The subject has been fairly intimately exposed to tuberculosis, but particularly so in August, 1910

This serum has been used in the technic many times prior to August and with one possible exception, when it was old, has always shown some evidence of inhibition Unfortunately, it happened that no reaction was made during September and October, the last two being on July 20 and 23 Further, the fourth cutaneous test is distinctly different in type and onset from the three previous, which have been more fully considered in the first publication It seems impossible to ignore, at the least, a diagnosis of biological or anatomical tuberculosis

As the reliability of these observations has increased, every endeavor has been made to check the life of the patient when a change in the serum reaction occurs From this one hopes to prove a distinct indication regarding the general handling of cases However, as can be seen from the remarks under Paragraph C and from theoretical considerations, an unfavorable turn in an inhibitive reacting case may not always be preceded or accompanied by a loss of that serum content While it is impossible to be certain that this has or has not occurred to some extent in the cases under my observation, no evidence of such has been noticed On the present theoretical grounds, a loss of tuberculin sensitiveness should accompany this particular retrograde tendency

#### *4 Cases Showing the Indifferent (Class 3) Serum Reaction*

This reaction has been found originally and confirmed in (a) definitely moribund cases and (b) others in which the main distinction seems to lie in their slightly plus and minus ability for slow local improvement with varied clinical response It has been followed in patients who have shown a loss of tuberculous sensitizers and inhibition, and, as far as chronologically ascertainable, may be associated in the former with local and general subsidence, or even improvement, while in the latter with unfavorable conditions both objectively and subjectively Further, these relations obtain with all varieties of tuberculin type reactions, so that the possible biological states seem confusing It is on contrast cases of this type, however, that one hopes to show immunological differences that

may be here marked, and which may play an unusual and effective rôle in those cases

As a result, one feels that pulmonary tuberculosis by itself presents three chief considerations for complete conception

- 1 The biological relations (or involvements) of host and infection
- 2 Anatomical involvement
- 3 Clinical response

These might be correlated as follows. The judgment of a case depends on one's conception of the biological interactions between host and the infecting tubercle, in consideration of the type, amount and duration of the anatomical involvement, and the resulting clinical response direct or indirect. One feels that all must be considered if one is to escape with the minimum of error in diagnosis, prognosis or treatment. The biological states can but roughly and approximately be estimated, as is also frequently true of the type and amount of anatomical involvement by our physical methods.

One feels that this is an attempt to interpret broadly biological or immunological data into clinical correlation without the almost essential qualification of presenting a critical clinical conception of many cases, and also submitting chronologically the laboratory end-results to a severe comparison with the details of the clinical history and charts. With the majority of cases of tuberculosis it seems necessary to present with their varying fluctuations, during long-drawn-out periods of time, many apparently small irregularities of clinical response and temperament, as well as the graver evidences of the infection, before one feels that the picture is sufficiently detailed. For this reason, only what seem to be the most important and clearest-cut examples have been given. These have been in the greater number of classifications repeatedly observed with slight variations. Clinical manifestations and anatomical involvement for correlation purposes can hardly be dealt with under simple classifications, nor can the biological data be summed up as positive or negative tests. These difficulties have underlain the presentation of the comparisons. The procedures began March, 1910, and up to October had been carried out on sixty-six cases to a greater or less extent, as the more experimental part of the work allowed their clinical application. Since then there have been eighty-four cases under as constant observation as the circumstances of the situation allowed, and the clinical variations in each case demanded. In this way, the serums from nearly all had been tested under many varying circumstances. As serums whose characteristics were determined have been used to further certain theoretical conceptions, frequent checks have been made on the same serum.

The clinical applications have proved to be valuable, and, as they exist the following considerations seem to be outstanding. With many cases

the occurrence of tuberculous sensitizers is significant, as this condition is in the majority of cases associated with clinical reverses and often acute setbacks with high temperature. Subsidence of the clinical response in a few cases sufficiently closely investigated has been followed by a disappearance of this serum content. Unusual opportunity for observation has demonstrated the great benefit of restricting cases of this type to rest in bed on the slightest appearance of fever, absolute rest being enforced and maintained if the temperature does not respond. The impression is very distinct that rest may be judiciously advised in many cases of this type even when there are no febrile disturbances.

Under favorable circumstances it has been possible to foreshadow both the favorable and unfavorable progress of a case by the come and go of the inhibitive reaction. In certain instances a disappearance of the inhibitive reaction has revealed not more than a stationary condition, in contrast to a previously favorable progress, or to a condition which one had previously conceived in a favorable light. These correlations have been most acutely marked in the early cases of slight involvement. This is proving of value in checking the life of arrested or improved cases in patients on their return to work.

Other aspects of tuberculosis seem to be affected by a consideration of these biological data, such as the administration of tuberculin and the selection of cases possibly suitable for other vaccine therapy, but I have attempted to present what seemed the most important, and have further confined myself to the results of those procedures relating to the humoral side of immunity. Certain possibilities relating to the cellular side are at present under investigation and promise results. One feels constrained to draw attention to this because the purely experimental side of immunity is passing into the hands of the chemical pathologist and physiologist, while the possibilities of the present knowledge are not being applied clinically. Neuberger in speaking of Hippocratic medicine writes "It is the conception of the medical vocation and the method of medical thought and action, true now as then, that distinguished that period." Would not advancement be materially aided if we regarded the application of immunology as a necessity for the treatment of the patient rather than a method of research?

# THE INCOAGULABLE NITROGEN OF PUNCTURE FLUIDS WITH SPECIAL REFERENCE TO CANCER

A PRELIMINARY NOTE

ROGER S. MORRIS, M.D.  
ST. LOUIS

To determine whether a collection of fluid in a serous cavity is of malignant origin is often a matter of considerable difficulty. The specific gravity and albumin content are of little or no value. The usual bloody nature of the fluid is not diagnostic. The only reliable means of detecting a malignant neoplasm from a study of puncture fluids alone has been the finding of mitotic cells—very rarely of tissue fragments—in the stained sediment, and such cells are often lacking.

In view of the demonstration of a proteolytic enzyme or enzymes in carcinomata and sarcomata, it occurred to me that the ferment, if secreted into a serous fluid, might disclose its presence by an increase in the quantity of incoagulable nitrogen. With this idea, the present study was undertaken.

That malignant tumors contain one or more proteolytic enzymes was first suspected by F. Müller.<sup>1</sup> That his surmise was correct has been demonstrated by the work of his pupils, notably Emerson,<sup>2</sup> Fischer,<sup>3, 4</sup> and Neubauer,<sup>4</sup> and by others. Petry<sup>5</sup> demonstrated that autolysis occurs in carcinomata, a fact which was confirmed by Neubeig<sup>6</sup> and by other observers. Buxton and Shaffer<sup>7</sup> proved the existence of a proteolytic ferment in cancers, the softer, more cellular tumors usually possessing it in greater abundance. Recently, Neubauer and Fischer<sup>4</sup> and Abderhalden

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<sup>1</sup>From the Clinical Laboratory, The Johns Hopkins University and Hospital.

1 Müller, F. Stoffwechseluntersuchungen bei Krebskranken, *Ztschr. f. klin. Med.*, 1889, **vi**, 496.

2 Emerson, C. P. Der Einfluss des Carcinoms auf die gastrischen Verdauungsvorgänge, *Deutsch. Arch. f. klin. Med.*, 1902, **lxvii**, 415.

3 Fischer, H. Zum Kenntnis des carcinomatösen Mageninhalts, *Deutsch. Arch. f. klin. Med.*, 1908, **xviii**, 98.

4 Neubauer, O., and Fischer, H. Ueber das Vorkommen eines peptidspaltenden Fermentes in carcinomatösen Mageninhalt und seine diagnostische Bedeutung, *Deutsch. Arch. f. klin. Med.*, 1909, **xviii**, 499.

5 Petry, E. Ein Beitrag zur Chemie maligner Geschwülste, *Beitr. z. chem. Phys. u. Path.*, 1902, **ii**, 94.

6 Neubeig, C. Chemisches zur Karzinomfrage, Ueber normale fermentative Vorgänge beim Krebs, *Berl. klin. Wchnschr.*, 1905, **xlii**, 118.

7 Buxton, B. H., and Shaffer, P. Enzymes in Tumors *Journ. Med. Research*, 1905, **xiii**, 543.

and his co-workers<sup>8</sup> have shown that malignant growths contain an enzyme capable of splitting certain polypeptids into their constituent amino-acids. This has led to the introduction by the first-named authors of the glycytryptophan test for the diagnosis of cancer of the stomach. With the demonstration, then, of a proteolytic enzyme in malignant neoplasms and of the secretion of the ferment into the stomach contents in gastric carcinoma, it is readily conceivable that primary or metastatic growths affecting the serous surfaces might secrete their ferment directly into the serous cavity and, therefore, into fluid occupying the cavity. Following the same line of reasoning, one would also expect to find an absence of the ferment in those fluids resulting merely from the pressure of tumors on important vessels. So that, at the outset, it was anticipated that an increase in the incoagulable nitrogen, if found, would not be met with in all cases.

The method used to remove the coagulable proteins was that of Hohlweg and Meyer,<sup>9</sup> slightly modified. The procedure is as follows. To 10 c c of the puncture fluid in a 300 c c Erlenmeyer flask one adds a reagent composed of equal parts of 1 per cent acetic acid and a 5 per cent solution of monocalcium phosphate until the reaction is acid to litmus but still neutral to Congo red. The limit is rather wide, varying from about 2 to 6 or more cubic centimeters with different fluids. Distilled water is now added to bring the volume to 80 c c and then 80 c c of saturated sodium chlorid solution are poured into the flask. The mixture is now boiled to precipitate the coagulable proteins and is then filtered through a folded filter directly into a Kjeldahl flask. The Erlenmeyer flask and filter are washed three times with distilled water. A Kjeldahl determination is made on the filtrate. Owing to the quantity of sodium chlorid contained in the latter, a considerable excess of sulphuric acid must be added to convert the sodium chlorid into sodium sulphate and still leave sufficient sulphuric acid for the oxidation. For this purpose about 30 c c of concentrated sulphuric acid is enough. Because of the preformed sodium sulphate, it is unnecessary to add potassium sulphate. Otherwise, the usual steps in the Kjeldahl method are carried out. All determinations are made in duplicate or triplicate, after a preliminary test of the filtrate has shown that the proteins are completely removed.

In all, twenty-five fluids have been available for examination up to the present time. The results are given in Table 1, the incoagulable

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8 Abderhalden, E., and Rona, P. Zur Kenntnis der peptolytischen Fermente verschiedenartiger Krebse, *Ztschr f physiol Chem*, 1909, **1**, 415, Abderhalden, E., Koelker, A. H., and Medigieceanu, F. Zur Kenntnis der peptolytischen Fermente verschiedenartiger Krebse und anderer Tumorarten, *Ztschr f physiol Chem*, 1909, **121**, 145.

9 Hohlweg, H., and Meyer, H. Quantitative Untersuchungen über den Rest stickstoff des Blutes, *Beitr z chem Phys u Path*, 1908, **11**, 381.

TABLE 1—INCOAGULABLE NITROGEN IN PUNCTURE FLUIDS (AUTHOR'S CASES)

No	Diagnosis	Incoagulable Nitrogen in gm per cent
1	Hydrothorax, chronic nephritis, arteriosclerosis	0 04585
2	Ascites, alcoholic cirrhosis of liver	0 0189
3	Hydrothorax, chronic nephritis, syphilis	0 0665
4	Ascites, ulcerative endocarditis, arteriosclerosis*	0 03395
5	Ascites, chronic peritonitis, luetic cirrhosis (?), valvular disease	0 0504
6	Pleurisy with effusion, pulmonary infarct, chr nephritis*	0 05425
7	Pleural effusion, cancer lung and pleura*	0 1162
8	Case 7, about five weeks later*	0 1120
9	Hydrothorax, mitral insufficiency, arteriosclerosis	0 03325
10	Tuberculous peritonitis†	0 0406
11	Case 1, five weeks later	0 0420
12	Pleural exudate (?), pulmonary tuberculosis, hypernephroma	0 05145
13	Pleurisy, lobal pneumonia (empyema developed four days later)	0 0805
14	Tuberculous peritonitis†	0 0399
15	Hydrothorax, chronic nephritis, myocarditis*	0 0529
16	Transudate, pleural (?)	0 03045
17	Tuberculous peritonitis†	0 0532
18	Pleurisy with effusion, pulmonary tuberculosis (?)	0 05005
19	Cancer of stomach, metastases in liver and peritoneum (?)‡	0 1099
20	Ascites, uterine fibroid (?)	0 0623
21	Ascites, mitral stenosis and insufficiency, chr nephritis	0 0413
22	Hydrocele fluid	0 0532
23	Cancer of liver, ascites (No metastases seen on peritoneum)†	0 0371
24	Hydrothorax, myocarditis, venous thrombosis*	0 0357
25	Hydrothorax, chronic nephritis, myocarditis	0 0504

\*Diagnosis confirmed at autopsy

†Diagnosis confirmed at operation

‡Typical case of gastric carcinoma Tumor at pylorus with stasis, lactic acid, Oppler-Boas bacilli, blood, positive glycyl-tryptophan test, palpable metastases in liver

nitrogen being expressed in grams per cent In the literature, no studies of the incoagulable nitrogen in the present connection have been found, but from observations on autolysis of exudates and transudates I have been able to collect a number of records from the publications of Umber,<sup>10</sup> Schutz,<sup>11</sup> Schulz and Muller,<sup>12</sup> Eppinger,<sup>13</sup> Galdi,<sup>14</sup> and Zak<sup>15</sup> (see Tables 2, 3, 4, 5, 6, 7, respectively) The entire material comprises seventy-eight observations on sixty-eight patients From a study of these values, it is evident that the incoagulable nitrogen of puncture fluids is subject

10 Umber, F Ueber autolytische Vorgange in Exsudaten, Munchen med Wehnschr, 1902, xlv, 1169

11 Schutz, J Besteht in Punktionsflussigkeiten Autolyse? Centralbl f inn Med, 1902, xxiii, 1161

12 Schulz, O, and Muller, L R Klinische, physiologische und pathologisch-anatomische Untersuchungen an einem Fall von hochgradigem Ascites bei Pfortaderthrombose, Deutsch Arch f klin Med, 1903, lxxvi, 544

13 Eppinger, H Ueber Autolyse in Punktionsflussigkeiten, Ztschr f Heilk, 1904, xxv (Abt f inn Med), 378

14 Galdi, F Ricerche sull' autolisi degli essudati e dei transudati, Clin med ital, 1905, xlv, 65

15 Zak, E Ueber Autolyse in Punktionsflussigkeiten, Wien klin Wehnschr, 1905, xlviii, 376

to considerable variation (Of the figures given by these writers, only those showing the *initial* amounts of incoagulable nitrogen [i e, *before autolysis*] are reproduced in Tables 2 to 7)

I have attempted to divide puncture fluids into three groups according to their content in incoagulable nitrogen, the grouping being provisional and subject to future revision Group I includes all fluids whose incoagulable nitrogen is 0.0699 gm per cent or less, Group II fluids having

TABLE 2—INCOAGULABLE NITROGEN FROM UMBER'S TABLE\*

No	Diagnosis	Incoagulable Nitrogen in gm per cent
1	Cystic abdominal tumors (autopsy)	0.0515
2	Tuberculous peritonitis (?)	0.0352

Umber, F. *Munchen med Wchnsch*, 1902, *xliv*, 1169

TABLE 3—INCOAGULABLE NITROGEN FROM SCHULZ'S TABLE\*

No	Diagnosis	Incoagulable Nitrogen in gm per cent
1	Ascites	0.07245
2	Ascites	0.02415
3	Ascites	0.03115
4	Pleurisy, tuberculous (?)	0.0294
5	Ascites	0.0303
6	Ascites	0.02753
7	Pleural exudate	0.0297

\*Schulz, J. *Centralbl f inn Med*, 1902, *xxiii*, 1161

TABLE 4—INCOAGULABLE NITROGEN FROM SCHULZ AND MULLER†

I	Portal thrombosis, ascites	0.0306
	Same case	0.0371
	Same case	0.0252
	Same case	0.0322
	Same case	0.0273
	Same case	0.0217
	Same case	0.0280
	Same case	0.0217

Schulz, O, and Muller, L. R. *Deutsch Arch f klin Med*, 1903, *lxxvi*, 544

TABLE 5—INCOAGULABLE NITROGEN FROM EPPINGER'S TABLE\*

No	Diagnosis	Incoagulable Nitrogen in gm per cent
1	Pleurisy, tuberculous	0.0630
2	Pleurisy, tuberculous	0.03460
3	Peritonitis, tuberculous	0.03587
4	Pyopneumothorax	0.0406
5	Pyopneumothorax	0.03640
6	Carcinomatous pleuritis	0.07000
7	Carcinomatous peritonitis	0.11000
8	Ascites, cardiac	0.02700
9	Ascites, cirrhosis of liver	0.0348

\*Eppinger, H. *Ztschr f Heilk*, 1904, *xxv* (Abt f Med) 378



TABLE 6—INCOAGULABLE NITROGEN FROM GALDI'S TABLE\*

No	Diagnosis	Incoagulable Nitrogen in gm per cent
1	Pleurisy, tuberculous	0 0563
2	Peritonitis, tuberculous	0 0435
3	Pleurisy, tuberculous	0 0300
4	Chylous ascites, cancer of pancreas and liver	0 0896
5	Ascites, cholelithiasis	0 0369
6	Pleurisy, tuberculous	0 0208
7	Cancer of peritoneum	0 0532
8	Banti's disease with cirrhosis and ascites	0 0359
9	Case 8, some weeks later (peritonitis?)	0 0406
10	Polyserositis (peritoneal)	0 1064
11	Cirrhosis of liver	0 0616
12	Cancer of stomach and peritoneum	0 0448
13	Case 12, five weeks later	0 0584
14	Cancer of pleura	0 0602
15	Cirrhosis of liver	0 07

\*Galdi, F Clin med ital, Milano, 1905, xiv, 65

TABLE 7—INCOAGULABLE NITROGEN FROM ZAK'S TABLE\*

No	Diagnosis	Incoagulable Nitrogen in gm per cent
1	Hydrothorax	0 04306
2	Pleuritis	0 02792
3	Pleuritis	0 01479
4	Ascites, nephritic	0 04139
5	Hydrothorax	0 01391
6	Ascites, chronic peritonitis, cirrhosis	0 04515
7	Ascites, cardiac	0 04113
8	Pleuritis	0 02436
9	Pleuritis	0 02368
10	Ascites, ovarian cysts (?)	0 0266
11	Ascites, tuberculous	0 03243
12	Pleuritis	0 03133

\*Zak, E Ueber Autolyse in Punktionsflussigkeiten, Wien klin Wehnsch, 1905, xviii, 376

TABLE 8—GROUP I INCOAGULABLE NITROGEN LESS THAN 0 0699 GM PER CENT \*

From Table 1	21 observations on 20 fluids
From Table 2	2 observations on 2 fluids
From Table 3	6 observations on 6 fluids
From Table 4	8 observations on 1 fluid
From Table 5	7 observations on 7 fluids
From Table 6	12 observations on 11 fluids
From Table 7	12 observations on 12 fluids
Totals	68 observations on 59 fluids
Cancers—Group I	5 observations on 4 fluids

TABLE 9—GROUP II INCOAGULABLE NITROGEN 0 07 TO 0 0899 GM PER CENT \*

From Table 1	1 observation on 1 fluid
From Table 3	1 observation on 1 fluid
From Table 5	1 observation on 1 fluid
From Table 6	2 observations on 2 fluids
Totals	5 observations on 5 fluids
Cancers—Group II	2 observations on 2 fluids

TABLE 10—GROUP III INCOAGULABLE NITROGEN 0.09 to 0.1+

From Table 1	3 observations on 2 fluids
From Table 5	1 observation on 1 fluid
From Table 6	1 observation on 1 fluid
Totals	5 observations on 4 fluids
Cancers—Group III	4 observations on 3 fluids

0.07 to 0.0899 gm per cent, and Group III 0.09 to 0.1 gm or more. Using this classification, the majority of fluids fall in Group I, i. e., sixty-eight observations in fifty-nine fluids. Group II contains only five fluids, while in Group III there are five observations on four cases (see Tables 8, 9 and 10). In analyzing the three groups with reference to cancer, one finds that Group I includes four of cancer out of a total of fifty-nine fluids, Group II, two cases out of five, and Group III, three out of four. It would thus appear—though I realize that the statistics are too small to permit of generalizations—that a puncture fluid with incoagulable nitrogen below 0.07 gm per cent is *probably* not of malignant origin. In Group II, one's suspicions of malignant disease would be strongly aroused while in Group III the probability of carcinoma would seem to be great. The single non-carcinomatous case included in Group III is one of "polyserositis" (No 10, Table 6). In explanation of this finding, there appear to be at least two possibilities, either that a non-carcinomatous fluid occasionally shows a very large amount of incoagulable nitrogen, or that the case was in reality one of malignant disease.

No explanation of the high incoagulable nitrogen in certain carcinomatous fluids can be given at the present time. It is highly probable, however, that it is the result of the action of a proteolytic enzyme. (The fluids have been tested for the presence of preformed tryptophan with negative result.) It is possible, too, that an anti-enzyme may account for the low values met with in some of the cancerous fluids. Both of these points are under investigation. An attempt is also being made to determine whether the application of this method to the blood may be of service in the recognition of malignancy.

1806 Locust Street

# THE INFLUENCE OF TEMPERATURE ON THE OUTPUT OF THE HEART

HEINRICH F WOLF, M D

NEW YORK

While investigating the influence of the viscosity of the blood on the output of the heart, I observed that the cardiac discharge depends in a large measure on the temperature of the fluid used to vary the viscosity. This observation prompted me to disregard secondary effects for the present and to determine, first of all, the relationship between the temperature of the blood and the cardiac output.

The output of the heart was ascertained in accordance with the method of Rothberger<sup>1</sup>. The heart was placed in an oncometer of glass, the changes in the volume of the heart being recorded by air transmission. Rothberger confined his measurements to the changes in the ventricles, the volumetric variations of which were obtained by covering the large orifice of the oncometer with a rubber membrane and by inserting the organ up to its auriculoventricular junction through a central opening in the membrane. Rothberger employed still another procedure. He placed the entire heart in the oncometer and fastened the pericardial membrane over the brim of the instrument. Although actual values for the output of the heart cannot be obtained in this manner, it is nevertheless readily possible to record any change in the filling of the entire organ. As I sought to determine solely those alterations in the output of the heart and in the pulse-rate which are induced by varying the temperature of the blood, it was not my object to obtain precise quantitative data regarding the amount of the blood discharged by this organ. After all, the cardiac output is very much influenced by outside factors, for example, by the size of the animal, and the general condition of the heart and vascular system.

The experiments were carried out on cats in ether narcosis. The cavity of the chest having been opened, the pericardial sac was reflected and the heart placed in the oncometer. I made use of an ordinary Marey tambour instead of a piston recorder. The carotid artery was then connected with a mercury-manometer. Cannulas were inserted in the femoral artery and accompanying vein. A short time before the beginning of the experiment, a certain quantity of blood was withdrawn from a second

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\*From the Physiological Laboratory of Columbia University, College of Physicians and Surgeons, New York.

<sup>1</sup> Rothberger. *Arch f d ges Physiol*, 1907, cxviii, 358. A similar method was devised by Henderson. *Am Jour Physiol*, 1906, xvi, 325.

cat and its coagulation prevented by means of hirudin. Immediately before each experiment, the blood of the first animal was also rendered non-coagulable by injecting a sufficient amount of the same substance intravenously. A coil condenser was then filled with the blood obtained from the second animal. The ends of this coil were subsequently connected with the cannulas in the femoral blood-vessels, in such a way that the arterial blood traversed first of all the coil, before it again entered the circulatory system. A thermometer was placed in the venous end of the coil, for the purpose of determining the temperature of the blood as it entered the circulatory system. The temperature of the blood as a whole could readily be altered by passing water of different temperature through the jacket of the coil.

Naturally the temperature of the blood recorded at the femoral vein differs somewhat from that at the sinus of the heart, because as the blood in the coil soon meets the blood of the general circuit, the temperature must be higher at the latter point of the vascular system, and again, if the blood has been cooled, we would expect the temperature near the heart to be higher than that at the condensor. The changes in temperature occur gradually, but a certain variation cannot be avoided, because the velocity of the flow through the condensor also differs. The total amount of blood present in the animal always remains the same, because the quantity escaping from the femoral artery is again diverted into the vein.

The experiments have proved conclusively that the lowering of the temperature materially lessens the output of the heart. This effect is clearly shown in Figure 1. The upper record represents the volume of the heart as written by the cardiometer, and the lower record the carotid blood-pressure. The time is given in seconds. This line serves as the abscissa for the blood-pressure.

Although a diminution in the pulse-rate appeared as a rule in consequence of the decrease in the temperature, the difference was not always striking. In some of the tests a change in the systemic blood-pressure also resulted, but the change did not conform strictly to the temperature. While a lowering of the temperature usually led to a slight increase in the blood-pressure, it also happened that this procedure induced a moderate decrease. It was also evident that very slight differences in the temperature suffice to produce very pronounced alterations in the output of the heart. Even changes in the temperature of the blood which remained within physiological limits were sufficient to influence greatly the work of the heart. Herein lies the significance of this observation.

While employing the method described by Lohman,<sup>2</sup> Rothman<sup>3</sup> came to the conclusion that increases in temperature produce a similar change

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2 Lohman Arch f d ges Physiol, 1907, cxviii, 260

3 Rothman Arch f d ges Physiol, 1907, cxx, 400

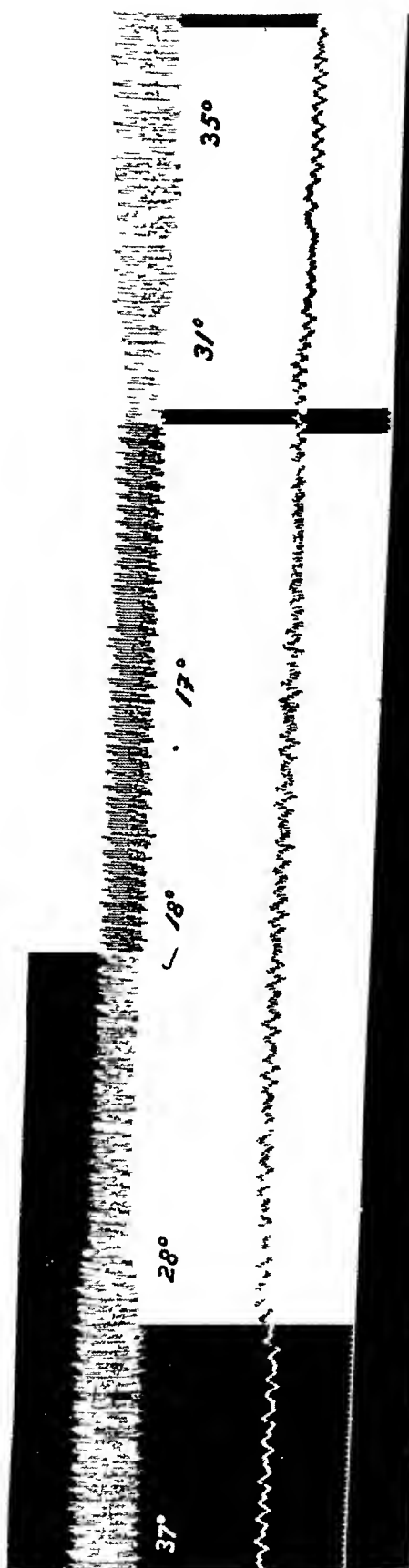


Fig 1—Infusion of cold blood. Pulse-rate 200 at 37 C and 136 at 17 C and again 164 at 35 C. The output decreases as the temperature is lowered and again increases. The blood pressure is slightly increased.

in the pulse-rate and in the work of the heart, hence these factors bear a direct relationship to one another. Heglin<sup>4</sup> and also Winkler<sup>5</sup> obtained similar results by estimating the work of the heart in terms of intra-auricular blood-pressure. In accordance with Heglin, the efficiency of the heart is increased by cold and decreased by hot douches. Although confirmed by Winkler, this observation is not seconded by Strassburger. I mention these experiments, but realize that they have no direct bearing

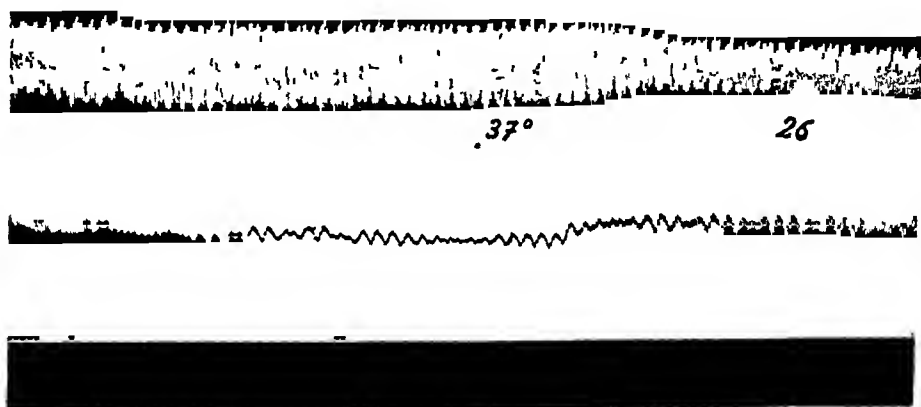


Fig 2—Both vagi were cut. Output decreased on cooling. Pulse rate decreased from 220 to 160. Blood pressure showed a slight rise.

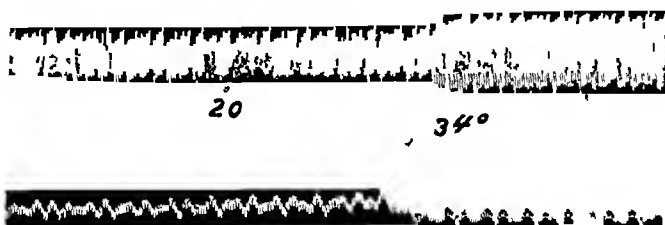


Fig 3—Both vagi were cut. Output increased on warming the blood. Pulse rate increased from 160 to 184. Blood pressure showed a slight fall.

on the question at issue here. In the first place, it is not proved that an actual change in the temperature of the blood results under the experimental conditions described in these papers and, secondly, numerous tests with isolated hearts have shown that the frequency of the beat varies with the temperature.

<sup>4</sup> Heglin. *Ztsch f klin Med*, 1894, *xxvi*, 15.

<sup>5</sup> Winkler. *Ztsch f klin Med*, 1904, *liv*, 92.

In endeavoring to find the cause of the variations in the cardiac discharge, I excluded, first of all, the influence of the nervous centers by severing both vagi. A comparison of the records taken before and after double vagotomy showed conclusively that this procedure has no influence on the cardiac output. A decided decrease was again obtained by cooling the blood, and an equally conspicuous increase by warming the blood. The changes here alluded to are clearly portrayed in Figures 2 and 3.

I also tested the effect of atropin in doses of  $\frac{1}{100}$  to  $\frac{1}{60}$  gr. The stimulation of the vagus nerve having become ineffective, the influence of changing the temperature of the blood was again determined as before. Results identical with those described previously were obtained.

The variations in the cardiac discharge and in the pulse-rate must, therefore, be dependent on a direct effect on the heart-muscle. The blood-pressure is not always affected in a manner corresponding to the temperature of the blood. When the temperature was lessened, the blood-pressure increased as a rule, while the warming of the blood was usually followed by a decrease. Evidently we are dealing in this case with a peripheral reaction, in that the cooling of the blood caused a constriction of the distal vascular channels and therefore also a rise in the general blood-pressure.

This fact is of importance in the treatment of infectious diseases, inasmuch as the work of the heart is a product of the output of the heart in a unit of time, in conjunction with the blood-pressure. The work of the heart increases, therefore, with the pulse-rate, the cardiac discharge and the blood-pressure. The results of these experiments permit the assumption that the work of the heart becomes greater during fevers, provided the blood-pressure remains constant. As fevers affect not only the peripheral blood-vessels but also those of the heart, the resulting impairment of the nutrition of this organ must become the more severe the greater the increase in the work of the heart.

Mention must be made at this time of the investigation of Yoshimura,<sup>6</sup> who has proved by thermo-electrical methods that the ventilation of the lung has a cooling effect on the heart. The blood leaving the pulmonary veins possesses a lower temperature than the cardiac substance and exerts, therefore, a cooling influence on this organ. If the escape of heat from the cardiac surface is prevented by enclosing the organ in cotton, the temperature of the cardiac muscle rises several degrees and the pulse-rate increases considerably. When infectious diseases and especially pneumonia, are treated in the open, the cool air entering the lungs lowers the temperature of the heart and lessens, therefore, the work of this organ by decreasing the cardiac output and the pulse-rate.

359 West One Hundred and Eighteenth Street

6 Yoshimura Arch f d ges Physiol, 1909, cxvii, 239

# EXPERIMENTAL CARDIORENAL DISEASE

HENRY A CHRISTIAN, M D, R M SMITH, M D, AND  
I CHANDLER WALKER, M D  
BOSTON

## INTRODUCTION

HENRY A CHRISTIAN, M D

During a period of about two years in the Laboratory of the Department of the Theory and Practice of Physic at Harvard we have been studying the lesions produced by certain chemicals known to have a particular action on the heart and kidneys. Different phases of this study have been undertaken by Dr. Smith, Dr. Walker and myself. In each case the topic has been studied by those whose names appear with the title and each study has been an independent one. However, as the topics are closely related and all form a part of a general investigation of cardiorenal disease, they are published together under the general title of Experimental Cardiorenal Disease as part of a series of studies of which three<sup>1</sup> have been published previously. It is hoped that by such a combined method of study—in the beginning, of experimental lesions, later, of the natural disease in man—some further light eventually may be thrown on that tangled complex which we frequently speak of clinically as cardiorenal disease. It will be evident to the reader of these papers that such a goal is far from attained, but some slight advance may be claimed from these experimental studies.

The general method followed in the present study has been to inject animals, chiefly rabbits, with varying doses of the drugs used, to follow the course of the disease so produced, and finally to autopsy the animals preserving all of the tissues for histological study just as is done with human autopsy material in a well organized pathological laboratory. Particular attention has been paid to the heart, the kidney and the liver though other tissues have been examined.

It has been quite evident to us that the substances used in this study, all of which have been employed by other investigators, have a remarkably

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<sup>1</sup>From the Laboratory of the Department of the Theory and Practice of Physic, Medical School, Harvard University.

1 Study I—Smith, R M. The Origin of Urinary Casts, An Experimental Study, Boston Med and Surg, Jour, 1908, clviii, 696. Study II—Christian, Henry A. A Glomerular Lesion of Experimental Nephritis, Boston Med and Surg Jour, 1908, clxix, 8. Study III—Christian, Henry A. Clinical Value of Recent Studies in Experimental Nephritis, Jour Am Med Assn, 1909, liii, 1792.



localized effect in that the marked action is on one organ with but slight action on other organs. Uranium nitrate, etc., have but little demonstrable action in producing lesions elsewhere than in the kidney, and so for spartem and adrenalin in relation to the heart. This makes it possible to control quite satisfactorily the experimental lesion. At the same time individual susceptibility in animals varies and other imperfectly understood factors enter to render difficult the regular production of chronic lesions, which in the main are what we must produce before animal experimentation will greatly aid us in obtaining knowledge of chronic cardiac and renal disease in man.

252 Marlborough Street



Fig. I—Camera lucida drawing of a glomerulus showing the type of degenerative lesion commonly found in acute uranium nitrate nephritis in the rabbit.

#### STUDY IV VASCULAR LESIONS OF ACUTE EXPERIMENTAL (URANIUM NITRATE) NEPHRITIS \*

HENRY A. CHRISTIAN, M.D., BOSTON

In 1908, under the title "A Glomerular Lesion of Experimental Nephritis"† I described certain changes found in the glomeruli of the kidney in rabbits which had received subcutaneous injections of uranium nitrate. These changes were found in eleven of a series of thirteen rabbits treated in this way.

The lesion described at that time is essentially a vascular lesion affecting the capillaries of the glomerular tuft and consists of a type of hyaline

From the Laboratory of the Department of the Theory and Practice of Physic Medical School Harvard University.

Reported at the Annual Meeting of the Association of American Physicians, May 9-10, 1911, Atlantic City.

†Christian Henry A. Boston Med. and Surg. Jour., 1908, cliv, 8.

degeneration of the wall of the capillary, as shown in Figure I The lesion was described as follows

The lesion consists of the appearance in the glomerular tuft of small, round or oval, rarely irregular, homogeneous dioplets, varying from a half to four microns in diameter. These dioplets appear in the wall of the capillaries making up the glomerular tuft, and do not occur either in the lumen of the capillaries or in the space between the glomerular tuft and the capsule of the glomerulus except in rare instances, when their position might be explained as an artifact in preparation. They were not found in the epithelium lining Bowman's capsule. In some glomeruli, only a few scattered dioplets occur, while in others they are very numerous. Very often in a glomerulus they tend to occur in groups of three to six or eight, and where the larger groups are found, almost always some of the droplets are considerably coarser than others of the same group. In some rabbits almost every glomerulus contains many dioplets of fairly large size, in others the dioplets are uniformly smaller. In some rabbits, some glomeruli contain numerous dioplets while adjacent glomeruli are free from them. This focal distribution seemed to have no relation to the other lesions of the kidney,



Fig II—Camera lucida drawing of a glomerulus from Rabbit 106 (acute uranium nitrate nephritis) showing fibrin thrombi in the capillaries of the glomerular loops

and no cause for it was to be made out. In kidneys showing slight degrees of the lesion, only here and there a glomerulus showed a few fine dioplets. The droplets which are here described stain intensely blue black with Mallory's phosphotungstic acid hematoxylin (hematein) stain, and resist decolorization with ferric chlorid for a long time. With eosin and methylene blue they stain pale red. The exact nature of the droplets is not known. Usually they can be distinguished quite easily from the somewhat more irregular granules associated with fibrin threads in the glomeruli.

As this degenerative lesion of the glomerular tuft is essentially a vascular lesion, and inasmuch as the recent studies of nephritis have tended to show that the edema of the disease is dependent on some vascular

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\*I am indebted to Miss Piotti for these drawings

injury and since the substance, uranium nitrate, which produces the above described glomerular lesion is the one which experimentally most frequently leads to the accumulation of fluid in the body cavities and subcutaneous tissues in association with renal lesions, it seemed desirable by a series of experiments to determine whether or not other demonstrable vascular lesions resulted from the use of uranium nitrate in rabbits. Consequently the following series of medium-sized rabbits were injected subcutaneously with 5 mg of uranium nitrate at periods of twenty-four hours, as shown in the following protocols:

Rabbits 100 and 101 were injected subcutaneously March 27 with 5 mg of uranium nitrate, and were killed twenty-four hours later.

Rabbits 102 and 103 were similarly injected on March 27 and 28, and were killed forty-eight hours after the first injection.

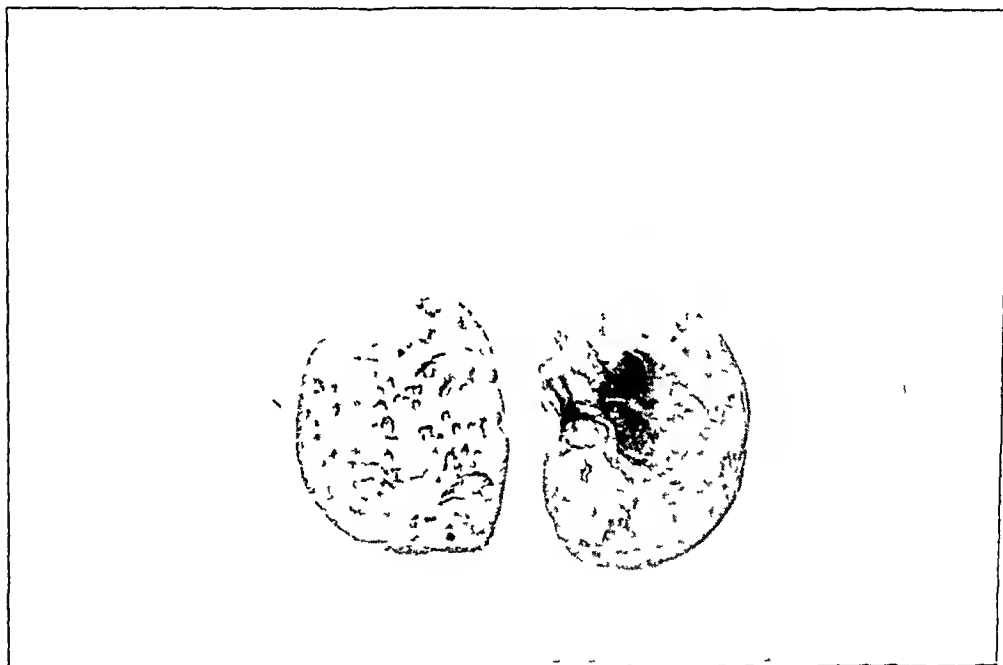


Fig 1—Rabbit 225, kidney shows slight irregularity of surface

Rabbits 104 and 105 were similarly injected on March 27, 28 and 29, and were killed seventy-two hours after the first injection.

Rabbits 106 and 107 were similarly injected on March 27, 28, 29 and 30, Rabbit 106 was found dead ninety-six hours after the first injection, and Rabbit 107 was killed ninety-six hours after the first injection.

Rabbits 108 and 109 were similarly injected on March 27, 28, 29 and 30, and were killed 120 hours after the first injection.

*Macroscopic Changes*—Of these rabbits, 100 and 101 showed at autopsy no departure from the normal. Rabbit 102 showed the usual amount of moisture in the body cavities, and scattered over the posterior portion of the peritoneal cavity numerous small subcutaneous hemorrhages of about pin-head size. Rabbit 103 showed a distinctly increased amount of moisture in the body cavities, and a small amount of free fluid

in the dependent portions of the peritoneal cavity. Rabbits 104 and 105 showed the same condition with respect to fluid, and in addition small hemorrhagic areas scattered in the peritoneal tissues. Rabbit 106 showed a moderate amount of free fluid in the peritoneal cavity. Rabbit 107 showed a very small amount of free fluid in the peritoneal cavity, and numerous small hemorrhagic points scattered over the surface of the kidney. Rabbits 108 and 109 showed a moderately increased amount of fluid in the body cavities.

*Microscopic Changes*—The following microscopic changes were noted in the kidneys of these rabbits.

In Rabbit 100 very slight degenerative changes in the tubular epithelium were made out but no lesions in the glomeruli.

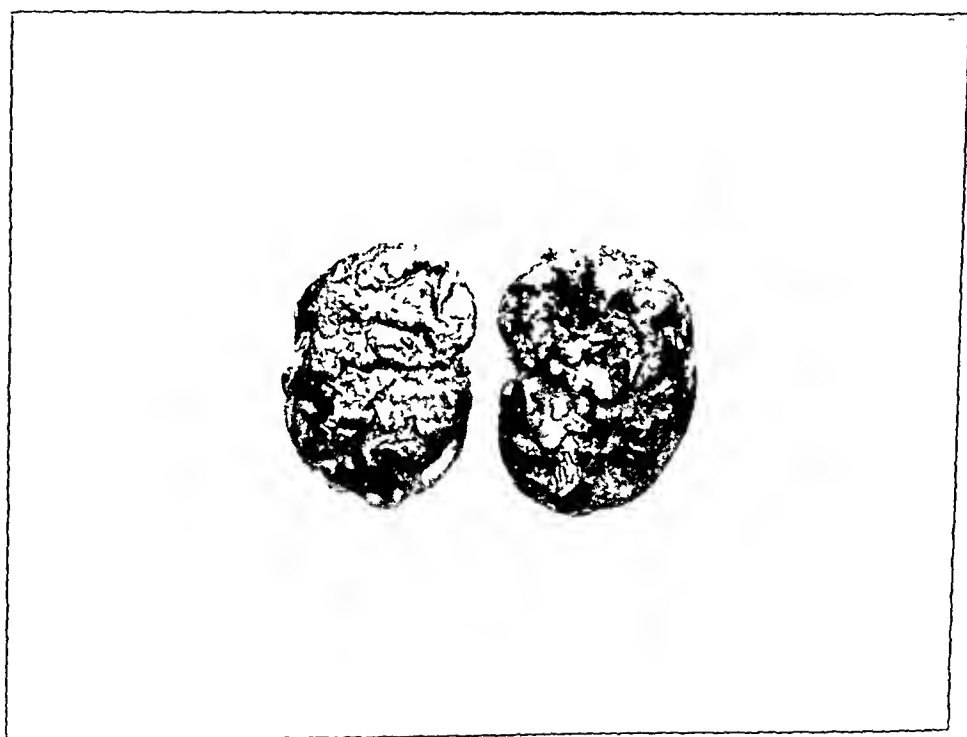


Fig. 2—Rabbit 257, kidney, gross specimen shows marked granularity and irregularity of surface of kidney.

In Rabbit 101 there was a more marked degree of degeneration of the tubular epithelium amounting to necrosis of the epithelial cells lining scattered tubules, and the presence in the lumina of the tubules of casts composed of desquamated, degenerated epithelial cells and granular material. No glomerular lesions could be made out.

In Rabbit 102 degenerative changes such as those described in Rabbit 101 occurred, but in very much more marked degree. In the glomeruli there was quite frequently present a small amount of granular material in the capsular space. The walls of the capillaries of the

glomerular tuft appeared to be distinctly swollen. The lumina of the capillaries were usually less evident than in the preceding rabbits. The glomerular tuft gave the impression of an increased cellularity. However, no actual evidence of cell proliferation was found in the glomeruli, though in the tubules occasional mitoses were seen, indicating that reparative changes were in process in the epithelial cells of the tubules.

Rabbit 103 showed the same lesions as those described in Rabbit 102, but distinctly less marked in degree than in Rabbit 102, though slightly more extensive than those described in Rabbit 101.



Fig 3—Rabbit 128. Kidney shows focus of marked cellularity infiltrated with neighboring focus of moderate connective tissue increase. Magnification 125 diameters.

Rabbit 104 showed the same changes as described in the preceding rabbits and in degree about equal to that found in Rabbit 102. In addition, the glomeruli in Rabbit 104 showed scattered in the walls of the capillaries of the glomerular tuft hyaline droplets as described in my earlier report (see Fig I). These droplets were present in the majority of the glomeruli and most of them were relatively coarse. In addition to these hyaline droplets staining darkly with the phosphotungstic acid hematein stain, the cytoplasm of the cells of the glomerular tuft was distinctly more granular than in the preceding animals. These granules

were fine, irregular, and stained rather palely compared with the dioplets. They resembled the general appearance of granules ordinarily found in the epithelium lining tubules of the kidney where there is only a moderate degree of degeneration present.

Rabbit 105 showed a very slight degree of tubular degeneration, not more than that shown in Rabbit 101, and no lesion was seen in the glomeruli.

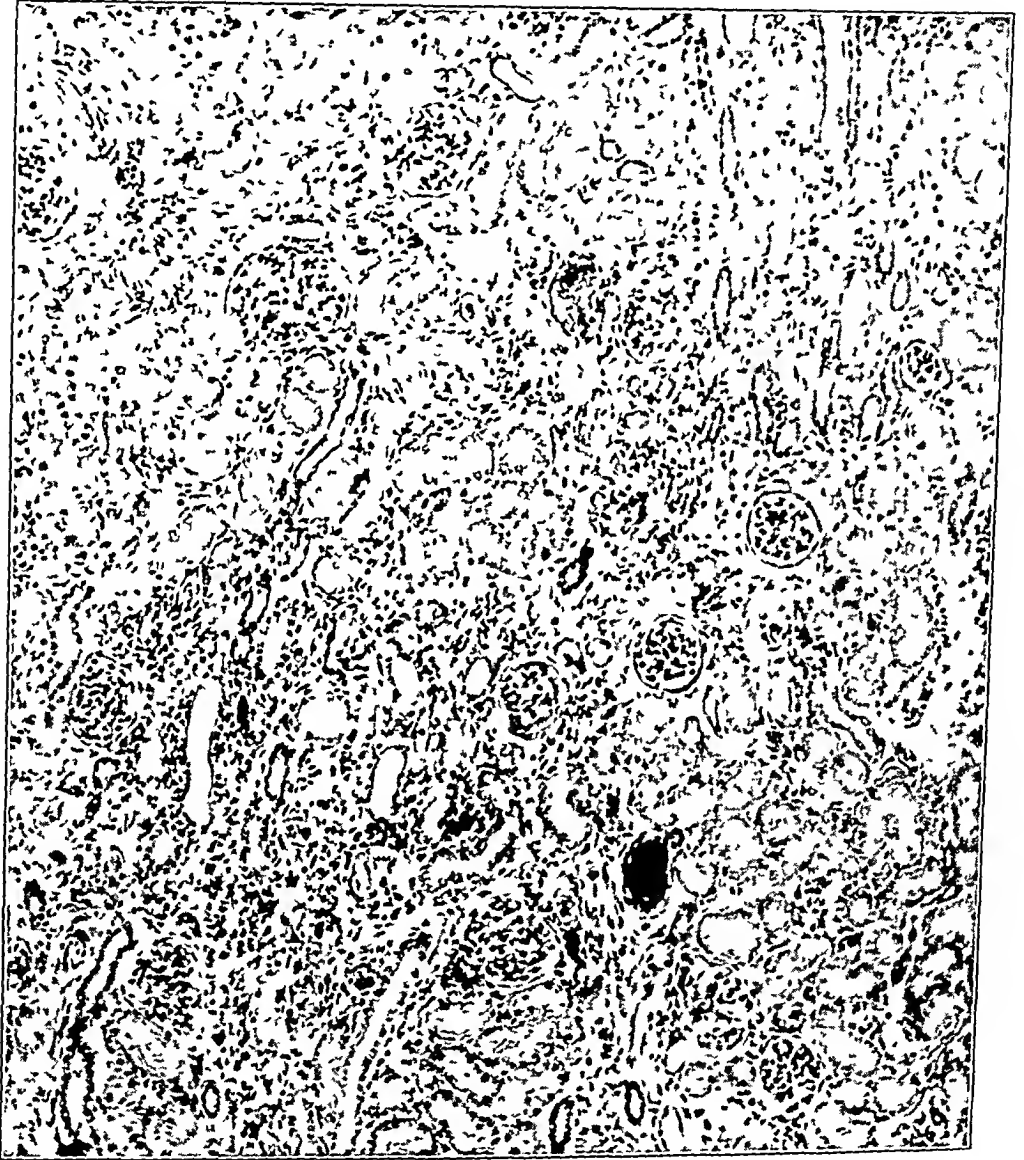


Fig 4—Rabbit 130. Kidney shows irregularly distributed areas of connective tissue increase in part fairly cellular. Magnification 146%, diameters.

In Rabbit 106 an extensive degree of degeneration and necrosis in the tubular epithelium were found. The glomeruli almost without exception showed the following lesion. The capillary loops nearly everywhere were filled with fibrin thrombi made up of rather coarse threads of fibrin which

very largely filled the lumen of the capillary as shown in Figure II. No hyaline droplets and no definite degenerative changes could be made out within the cells lining these capillaries. Except for the glomerular lesion, this kidney was similar to that from Rabbit 104. A lesion similar to this thrombosis of the capillary loops of the glomerulus was not found in any other of this series of rabbits, nor was it present in any of the other rabbits tabulated at the end of this paper. Up to the present time no satisfactory explanation for this variation in lesion has been found nor

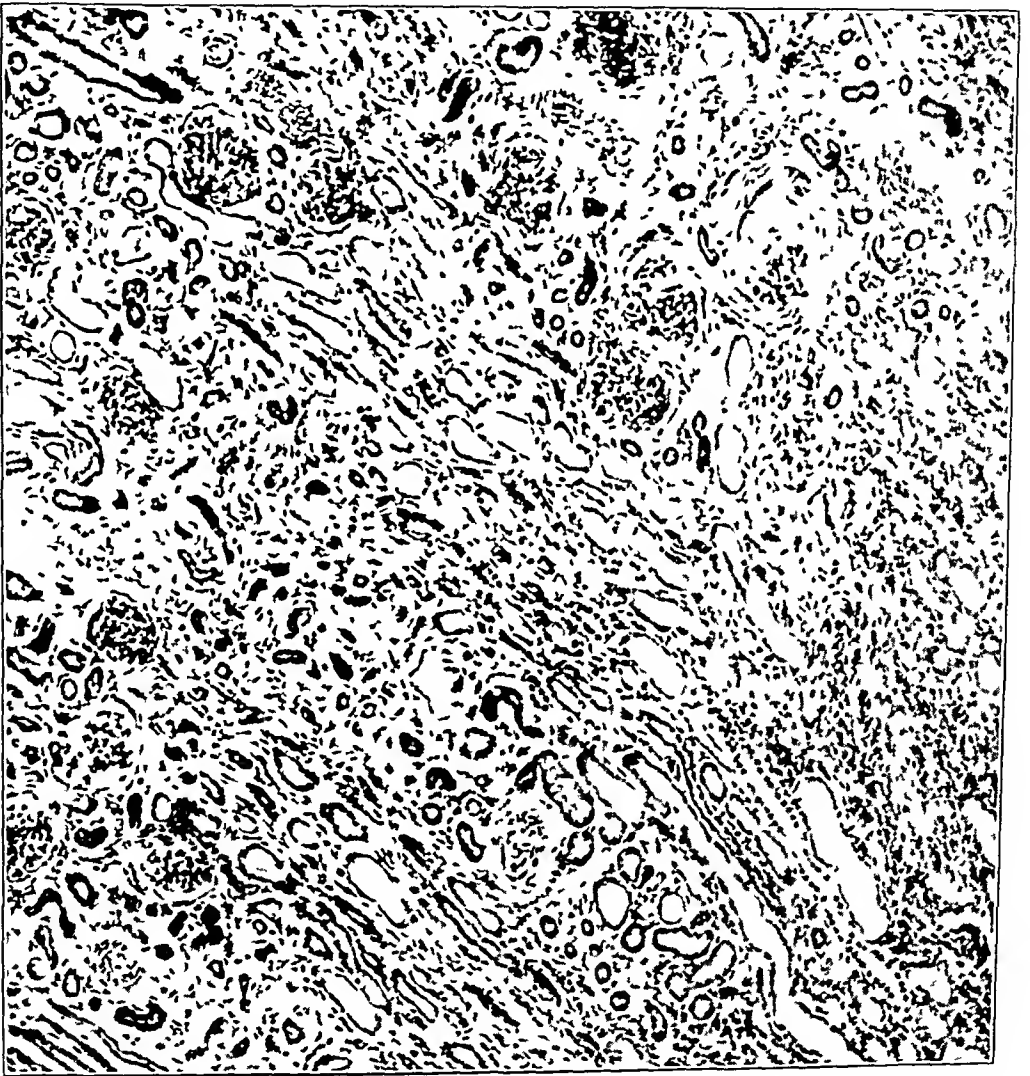


Fig 5—Rabbit 190. Kidney shows connective tissue increase with atrophy of tubules and sclerosis of glomeruli.

has it been possible to repeat this particular type of glomerular lesion by varying in several ways the conditions of the experiment.

In Rabbit 107 degenerative changes similar in nature to those described in Rabbit 104 were found. Hyaline droplets appeared in the glomerular tufts in the same way, but a rather larger percentage of glomeruli in Rabbit 107 failed to show the droplets than was the case in Rabbit 104.

Rabbit 108 showed extensive degenerative changes in the tubular epithelium, and the presence of many hyaline droplets in the walls of the glomerular tuft

Rabbit 109 showed changes very similar to those described in Rabbit 108, including hyaline droplets in the walls of the glomerular tuft

In this series of ten rabbits, definite vascular lesions occurred in the glomeruli of five animals. As a functional vascular injury has been assumed to be the cause of the edema of nephritis, it would seem probable that some demonstrable anatomical evidence of this lesion might be found by using the same technical method that demonstrates so well the above described glomerular lesion, a lesion hitherto overlooked. However, a

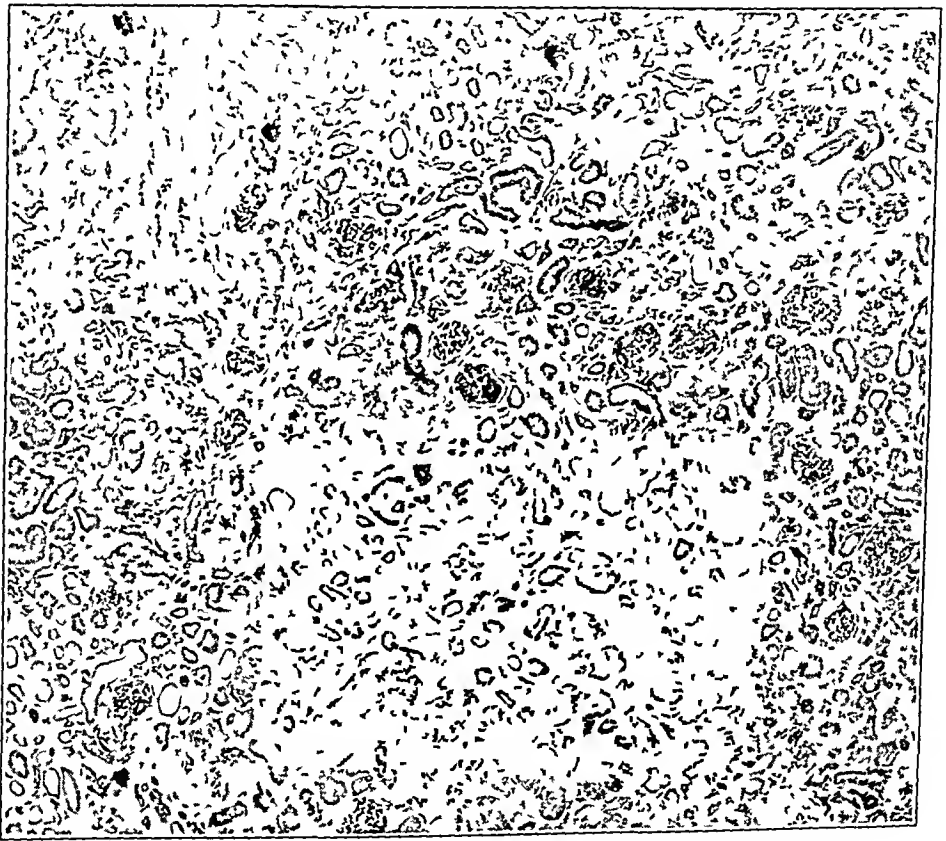


Fig. 6—Rabbit 226. Kidney shows connective tissue increase

very careful study of the small vessels of the kidney other than those of the glomerular tuft, failed to show any demonstrable lesion, either with the phosphotungstic acid hematein stain, or with the eosin methylene-blue stain, or the elastic tissue stain of Verhoeff. In addition to the kidney, the heart, liver and the spleen were studied by these same methods, but no demonstrable lesion was found in the blood-vessels of any of these organs.

Small arteries and veins as well as capillaries in sections of tissues are not easy of examination owing to their very thin walls which present



very little surface for study in any given section. In the capillary tuft of the glomerulus, the same conditions do not hold because there, with the convoluted course of the capillaries and the large number of loops aggregated together, a very considerable surface of capillary wall presents for examination. It seemed possible that this fact might be an explanation of finding anatomical lesions in the capillaries of the glomerulus and failing to find them in other vessels of relatively the same size.

In order to get small blood-vessels more suitable for microscopic examination, the mesentery was selected, inasmuch as here numerous small vessels run in an exceedingly thin tissue which, with proper precautions,



Fig 7 —Rabbit 129. Kidney shows a focus of connective tissue increase with almost complete disappearance of the tubular structures and persistence in the glomeruli. Magnification 125 diameters.

can be prepared and stained without sectioning, so that a good view may be had of the small vessel in longitudinal optical section, thus revealing clearly all of the cells and tissue that go to make up the vessel-wall. Instead of cutting sections of this tissue, the mesentery was prepared by stretching it over the end of bottle tops and tying it in this position. The bottle top with the attached bit of mesentery was then fixed in Zenker's fluid and carried through the various staining procedures. Stretched over

the bottle top the mesentery was prevented from shrinking and remained flat and smooth. After the staining was completed and the mesentery dehydrated in alcohol, with fine scissors rectangular bits of the mesentery were cut away, cleared in xylol, and mounted in balsam, just as would be done with a celloidin section.

By selecting thin bits of the mesentery containing small blood-vessels it was found possible to study very thoroughly the walls of such vessels. In them, however, no lesions in any way analogous to those found in the capillary tuft of the glomeruli could be made out. Since in these rabbits not infrequently there is a considerable amount of free peritoneal fluid,



Fig 8—Rabbit 245. Kidney shows an area of quite dense connective tissue extending in from the surface of the kidney as a scar. This connective tissue very largely replaces renal elements. The glomeruli are more resistant than the tubules. Magnification 125 diameters.

it might be supposed that these vessels contributed to the accumulation of fluid, and in them should be found an anatomical lesion corresponding to this assumed functional lesion. However, this was not the case, or in other words, the methods of fixation and staining utilized did not succeed in demonstrating any anatomical lesion of these blood-vessels.

Thinking it possible that some larger blood-vessels might show a lesion, in all of these rabbits the aorta and inferior vena cava were ligated

so as to be distended with blood, and were fixed in Zenker's fluid in this condition. Subsequently, cross-sections of these distended vessels were embedded and stained in the various ways described above. Histological study of these, however, failed to show any anatomical lesion.

As a result of these studies, it is seen that the only anatomical lesion of the blood-vessels found in association with the renal lesions produced

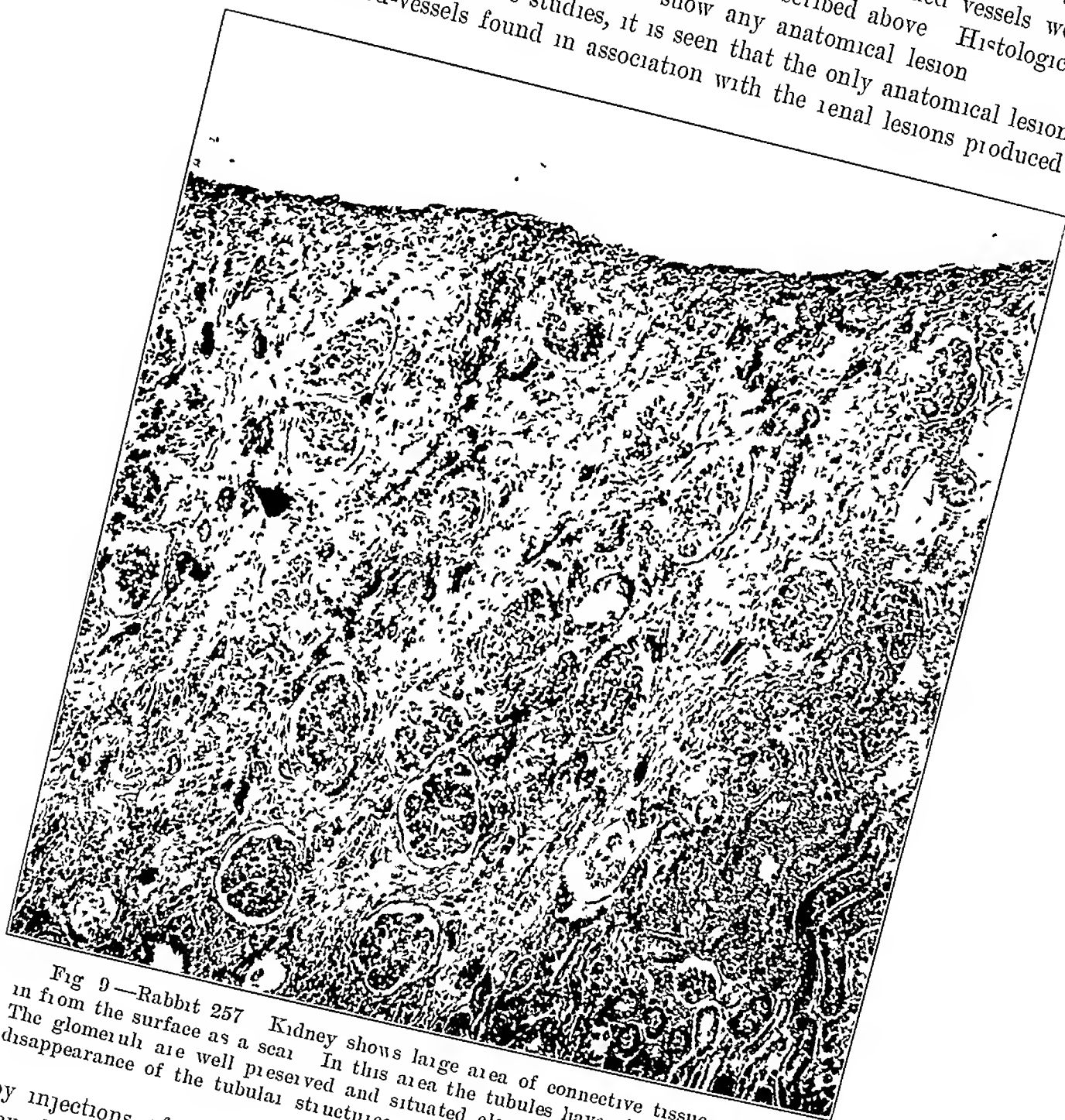


Fig. 9—Rabbit 257. Kidney shows large area of connective tissue extending in from the surface as a scar. In this area the tubules have almost disappeared. The glomeruli are well preserved and situated close together as a result of the disappearance of the tubular structures. Magnification 146½ diameters.

by injections of uranium nitrate occurs in the glomerular tuft. The causal relation of this lesion to the uranium nitrate is shown in the following table, Table A, which gives the amount of uranium nitrate and the frequency of dose which produced this lesion in rabbits.

TABLE A — RELATION BETWEEN LESIONS AND URANIUM NITRATE

No of Rabbit	Weight of Rabbit gm	No of Doses of Uranium Nitrate	Total Amount of Uranium Nitrate gm	No of Days Between First Dose and Autopsy of Animal	No of Days Between Last Dose and Autopsy of Animal	Lesion in the Glomerulus
1	1350	3	015	3	1	+
2	635	3	012	3	1	+
3	825	3	012	3	1	+
4	725	3	012	3	1	+
5	1040	1	005	1	1	0
6	730	2	010	2	1	+
7	1020	1	005	5	5	+
8	720	1	004	4	4	+
9	930	2	004	6	4	+
10	800	3	003	17	21	0
11	985	1	001	6	6	+
21	1950	1	001	6	6	+
22		9	013	110	15	0
71	2095	4	0035	130	11	0
72		1	001	6	6	0
73		1	001	5	5	0
100		1	005	1	1	0
101		1	005	1	1	0
102		2	010	2	1	0
103		2	010	2	1	+
104		3	015	3	1	0
105		3	015	3	1	+
106		4	020	4	1	+
107		4	020	4	1	+
108		4	020	5	2	+
109		4	020	5	2	+
123		5	021	6	1	+
198	1190	1	005	5	5	0
199	1140	1	005	5	5	+
200	1190	1	005	5	5	0
221	1460	22	044	90	21	0
226	1310	7	014	33	2	0
240	2800	1	005	6	6	+
249	1720	4	020	60	3	0
251	1690	1	005	7	7	+
259	1500	4	008	18	7	0
190	1390	3	015	44	11	0
128		2	010	33	16	0

\*The lesion here referred to is the occurrence of hyaline droplets in the wall of the capillary of the glomerulus as described above. The only exception to this is in Rabbit 106, where the lesion consists of the occurrence of fibrin thrombi in the capillaries of the glomerulus.

## SUMMARY

In acute experimental nephritis produced by subcutaneous injections of uranium nitrate, there occurs in the glomerulus a degenerative condition consisting usually of the appearance of hyaline droplets of varying size in the wall of the capillary. In the other small vessels of the kidney and the small vessels of the heart, liver and spleen, and in the small vessels of the mesentery, no anatomically demonstrable lesion could be made out. The vascular lesion of this type of acute nephritis, as far as

could be demonstrated by the technical methods employed, is confined to a vascular structure of specialized function, a more highly differentiated structure than that of other small blood-vessels, namely, to the capillary loops of the glomerulus

#### STUDY V EXPERIMENTAL CHRONIC NEPHRITIS

R M SMITH, M D, BOSTON

The literature of experimental nephritis has been so recently and so fully discussed by Christian,<sup>2</sup> Pearce,<sup>3</sup> and others,<sup>4</sup> that I shall not enter into any consideration of it here, nor shall I discuss the problems arising in connection with the experimental work. In the course of the investigations cited in this paper many acute lesions were produced, animals died before chronic lesions were formed, or the acute lesion obscured the picture of a coincident chronic process. The study of these acute conditions has not shown anything new, and therefore their consideration is omitted. It has been possible, however, to produce certain chronic changes in the kidney, which I shall describe in some detail, together with an account of the methods employed in their formation.

The experiments were carried on in the laboratory of the Department of the Theory and Practice of Physic, under the direction of Dr Henry A Christian. The animals used were rabbits and guinea-pigs. The latter in my hands proved very unsatisfactory, the greater part of the work is therefore based on the lesions as seen in rabbits. Ninety-five animals were employed, eighteen were carried through a period of three weeks to three months, and fifty-six through a period of three months or over. The remainder died of acute lesions or of some intercurrent disease, usually pneumonia. Most of the animals were allowed to go a number of weeks without injection previous to killing to exclude any acute lesion.

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From the Laboratory of the Department of the Theory and Practice of Physic, Medical School, Harvard University.

\*This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

<sup>1</sup>Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D C.

<sup>2</sup>Christian. Experimental Nephritis, Boston Med and Surg Jour, 1908, cxxviii, 416. Clinical Value of Recent Studies in Experimental Nephritis, Jour Am Med Assn, 1909, lxi, 1792.

<sup>3</sup>Pearce. Problems of Experimental Nephritis, THE ARCHIVES INT MED, 1910, v, 133.

<sup>4</sup>Dickson. A Report on the Experimental Production of Chronic Nephritis in Animals by the Use of Uranium Nitrate, THE ARCHIVES INT MED, 1909, iii, 375. Emerson. An Experimental and Critical Study of the Etiology of Chronic Nephritis, THE ARCHIVES INT MED, 1908, i, 485. Lyon. Experimental Nephritis, Jour Path and Bacteriol, 1904, ix, 400. Ophuls. Some Interesting Points in Regard to Experimental Nephritis, Jour Med Research 1908, viii, 497. Ophuls. Chronic Experimental Nephritis Jour Am Med Assn, 1907, xliii, 483.

Three drugs were used—mercuric nitrate, potassium bichromate and arsenic, in the form of Fowler's solution. No other drugs were tried because it was felt that it would be best to have a larger number of observations of lesions produced by a few drugs, from which more accurate conclusions might be drawn.

The question of dosage was a matter to which considerable attention was given and no little experimentation. It was found for a rabbit of average weight (1,500 to 2,000 gm.) 5 mg. of mercuric nitrate was as much as it was safe to give, since larger doses killed the animals in many

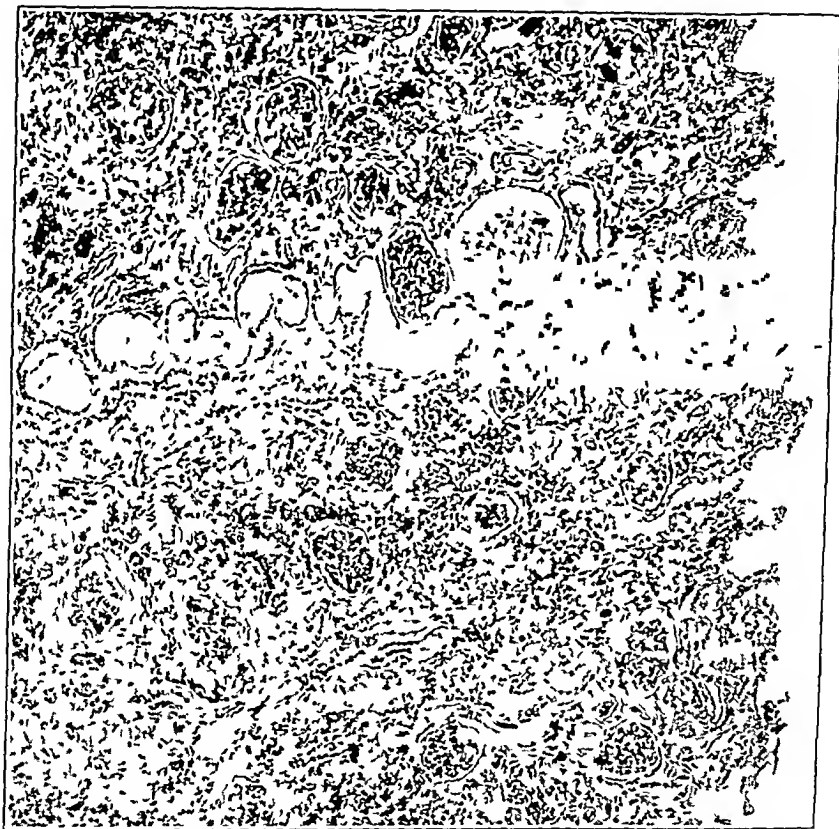


Fig. 10—Rabbit 129. Kidney shows marked dilatation of one tubule, moderate dilatation of the glomerular space in one glomerulus, with surrounding connective tissue increase and atrophy of tubules.

instances. This dose gave a rather severe acute nephritis, but the great majority of the animals survived. By following the first-used animals very carefully it was found that in about three weeks the urine was nearly normal, i. e., the attack of acute nephritis was nearly over. This interval, three weeks, was taken, therefore, as the time at which the injections were to be repeated. Another method of employing this drug was to give very frequent small doses. For this purpose 2 mg. every three days were used. The comparative results of the two methods of injection will be discussed later. Potassium bichromate was used in a 1 per cent solution. Here also the size and frequency of dosage was determined by experimentation.

and 0.0125 gm of potassium bichromate every three weeks was decided on as the most satisfactory. Fowler's solution was given in from 8 to 10 minim doses, subcutaneously, and by stomach-tube, repeated every three weeks.

In guinea-pigs, for some reason or other, it was impossible to use the doses of uranium nitrate reported by others. More than 0.5 mg for an average-sized guinea-pig was fatal in most cases. One-half milligram every three weeks was therefore used. Perhaps the smallness of the dose in some measure accounts for the unsatisfactory results. Bichromate of

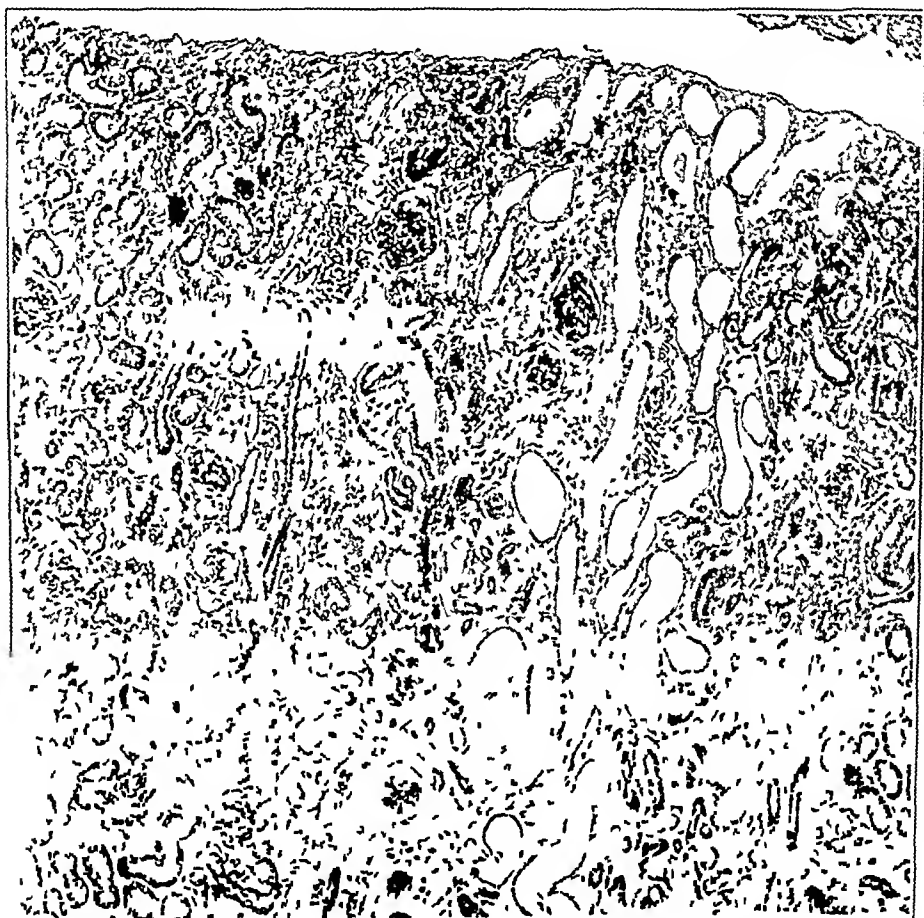


Fig. 11.—Rabbit 221. Kidney shows area of connective tissue increase with marked dilatation of a group of tubules. Magnification 125 diameters.

potassium was given, 0.005 gm every three weeks. No guinea-pigs were tried on Fowler's solution.

Beside the animals used in these experiments, fifty rabbits were studied to exclude the possibility of the conditions described being due to spontaneous lesions. Some lesion was found in eleven of these fifty rabbits, or 20 per cent. The lesions when found consisted in almost every instance of a single area of round-cell infiltration, connective tissue increase or a small group of dilated tubules. Six of the sections showed such a slight variation from normal as to be practically negligible.



Another showed nothing but a connective tissue increase. Two showed moderate dilatation of tubules, but little else. The remaining two showed well-marked lesions—one of the animals had had intravenous injections of spartein sulphate and adrenalin (epinephrin) chlorid every day for two months. The experimental rabbits having uranium nitrate and potassium bichromate injections running over three months from the time of the first injection to the time of autopsy, thirty-nine in number showed lesions of one form or another in thirty-six cases or 92.3 per cent. Seven guinea-pigs were similarly treated and four or 57.1 per cent showed lesions. The percentage of experimental rabbits having lesions is so large,

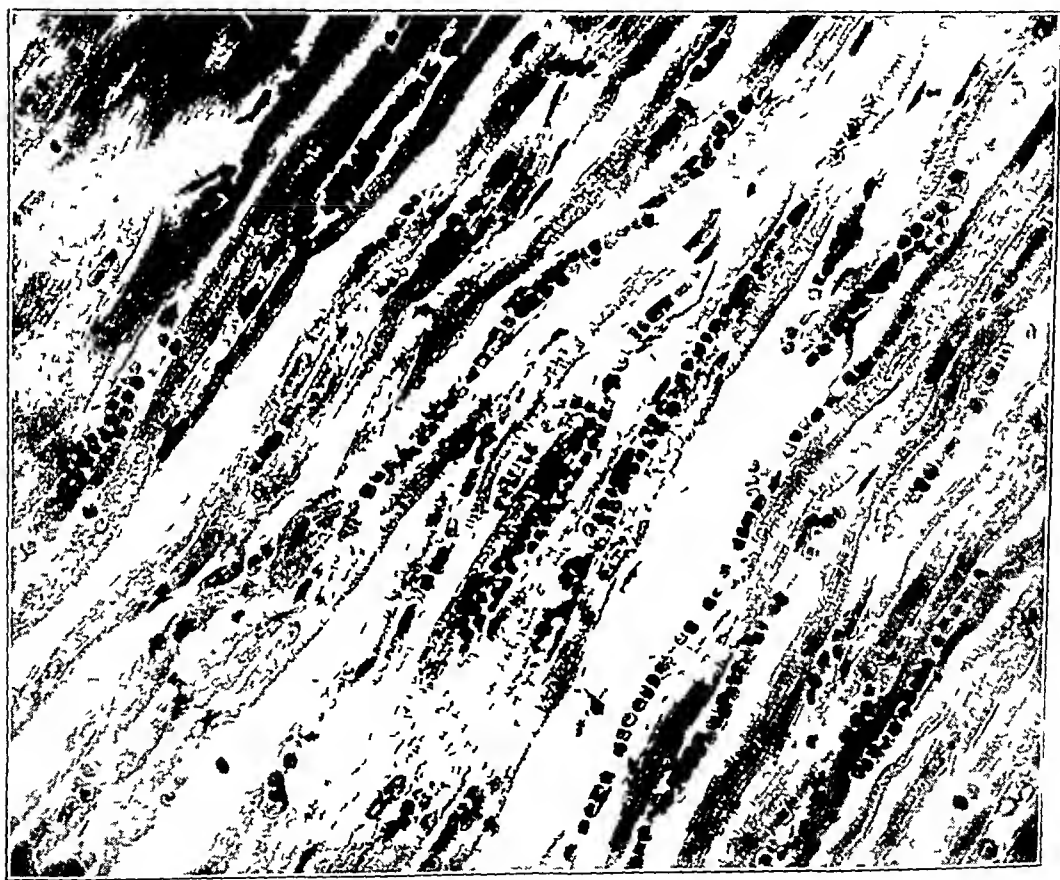


Fig. 12—Rabbit 268. Section shows myocardium with marked congestion of capillaries. Magnification 185 diameters.

the percentage of controls with lesions so small and the lesions so insignificant when present, that it makes it impossible to assume that the lesions in the experimental animals were other than the result of the injections given. The chronic lesions caused by uranium nitrate and potassium bichromate were the same, and will therefore be described together.

Three side-studies, so to speak, were made on this series of animals (1) the weights of heart and kidneys in relation to the body-weight of the



animal and in relation to each other, (2) the effect of sodium chloride and water in the production of edema, (3) a functional test in excreting phenolsulphonephthalein. These investigations are considered separately in other papers and are therefore only mentioned here.

The kidneys, macroscopically, were, in most cases, normal in appearance and in all the capsule stripped easily. On section the markings were distinct and the cortex not narrowed. In some the surface was covered with many irregular, smaller and larger depressions and on section bands of fibrous tissue could be seen running down into the substance of the organs. These macroscopic lesions occurred principally in the animals

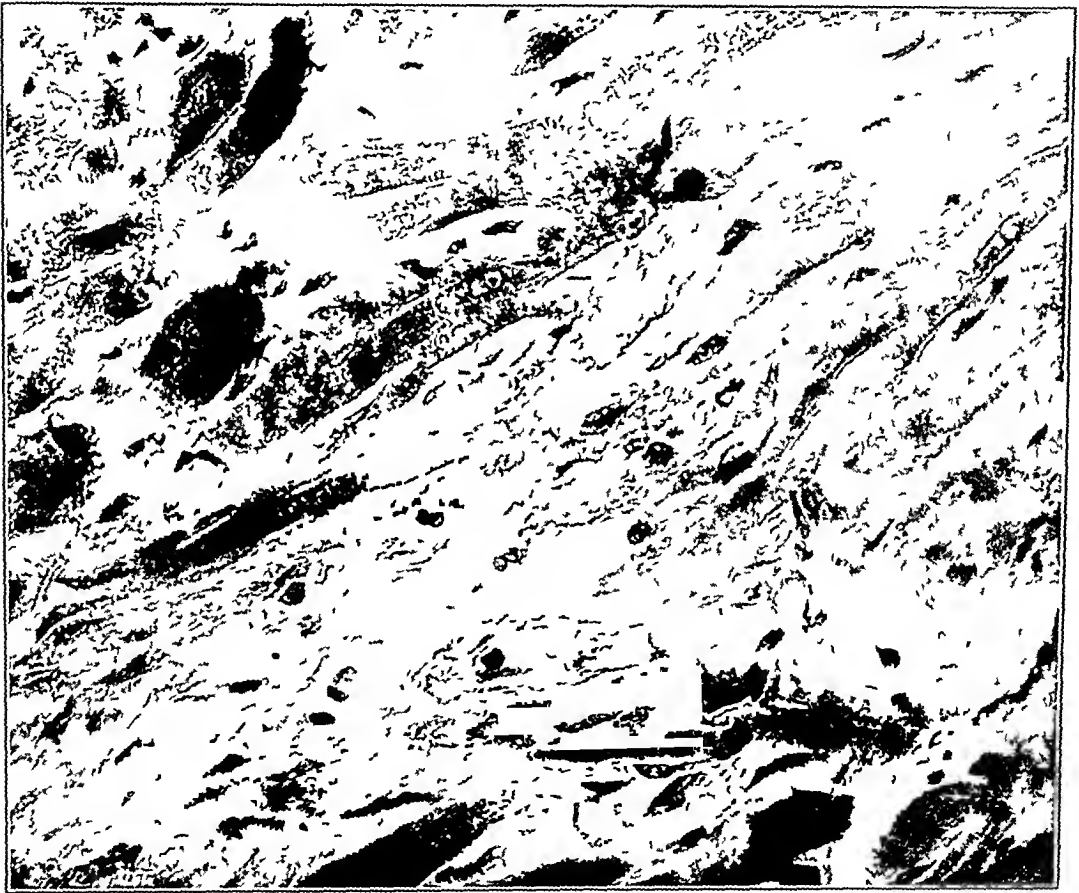


Fig 13—Rabbit 266. Section shows a portion of myocardium with interstitial edema and moderate connective tissue increase. Magnification 185 diameters.

that had received potassium bichromate (Rabbit 225, Fig 1, and Rabbit 257, Fig 2).

Microscopically variations from the normal were seen in three main particulars. The most frequent abnormality was round-cell infiltration. This occurred in the animals which had received uranium and bichromate injections, but most consistently in those receiving the large doses of uranium. The areas of infiltration, though often very small, were frequently of considerable size. Their location was variable but they were

most often found in the cortex and in the larger number of cases near the periphery (Rabbit 128, Fig 3, also Rabbits 177, 189 and 195)

Beside this infiltration of round cells, in a certain number of animals there was formation of definite connective tissue. The connective tissue for the most part was fairly young (Rabbit 130, Fig 4), but in some instances was old, having gone on to a fibrous tissue stage (Rabbit 190, Fig 5, and Rabbit 226, Fig 6). The distribution of the connective tissue was usually near the periphery of the organ. It often was so extensive as to replace entirely the tubular portion of the kidney over considerable areas, leaving a few tubules in the center as a small island (Rabbit 129,

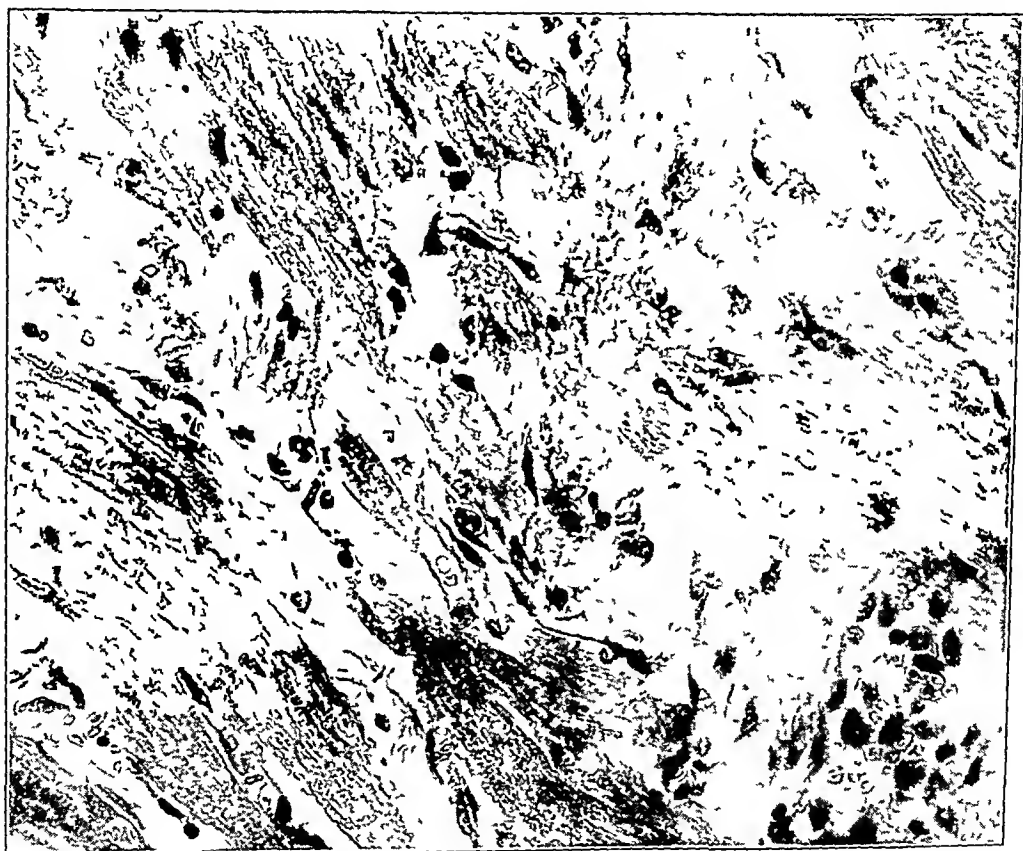


Fig 14—Rabbit 79. Section shows moderate connective tissue increase, edema, and moderate cellular infiltration of the myocardium. Magnification 185 diameters.

Fig 7). Usually in sections showing an increase in connective tissue the connective tissue was seen as triangular foci running into the substance of the organ from the periphery with the apex inward. It was these fibrous bands which were found in connection with the macroscopic depressions on the surface of the kidney (Rabbit 245, Fig 8; 257, Fig 9, see also Rabbits 124, 207, 208 and 264).

The most distinctive lesion which was found, a lesion closely resembling that associated with chronic interstitial nephritis in man, was a

dilatation of the convoluted tubules and glomerular spaces. This occurred for the most part in sections which showed the other two conditions and most frequently in those animals which had had large doses of the drugs. The dilatation was patchy in distribution as were the areas of round-cell infiltration and was most often located in that portion of the cortex directly beneath the capsule. The glomerular spaces showed much less dilatation than the tubules (Rabbits 129, Fig 10, and 221, Fig 11, see also Rabbits 192, 193 and 196).

In the animals which had received arsenic, macroscopic examination of the kidneys showed nothing abnormal. Microscopically the kidney

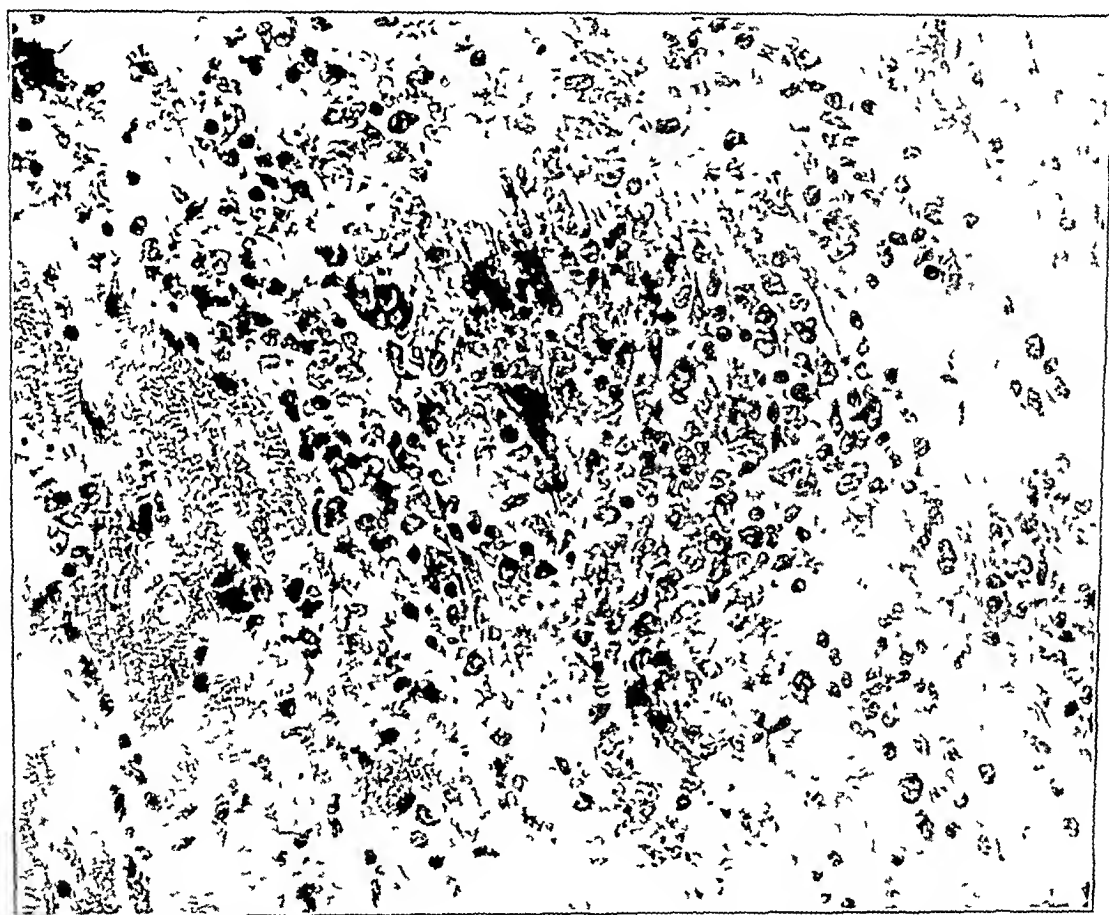


Fig 15—Rabbit 279. Section shows a very cellular focus of proliferation in the myocardium. Magnification 185 diameters.

sections from animals which had received the drug by mouth showed nothing, and in those given subcutaneous injections the only change seen was distinct congestion of the glomeruli without any apparent damage to the endothelium. In the cases where no injection had been given for a long time there was a little increase in the number of cells in the glomeruli. These findings are in accord with the reports of other investigators (Rabbits 233, 238, 243).

To reiterate in conclusion, to produce the more distinctive lesions of chronic interstitial nephritis experimentally the best results will be obtained by using as large doses of uranium nitrate and potassium bichromate as the animals will stand, repeated at three week intervals for three months or longer. Bichromate of potassium produces more fibrous tissue formation with macroscopic depressions on the surface of the kidney than uranium nitrate. Small frequent doses of uranium nitrate cause patchy round-cell infiltration throughout the cortex of the kidney and much increase in connective tissue. Aisemic produces no chronic macroscopic or microscopic lesion of the kidney, except congestion and slight increase of cells of the glomeruli.

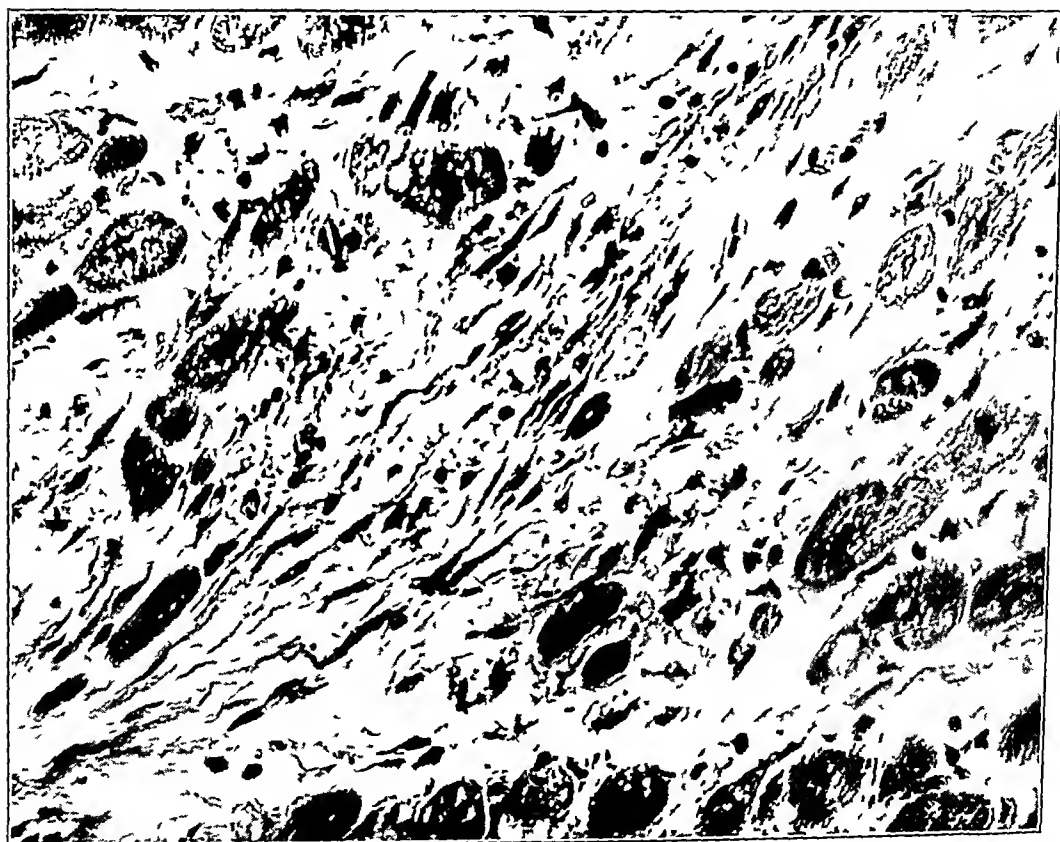


Fig 16—Rabbit S2. Section shows myocardium infiltrated with new connective tissue, fairly cellular, which separates muscle fibers. Magnification 185 diameters.

The protocols of the animals follow

PROTOCOL 124—Rabbit. Weight 1870. Caged October 12. On 13th given 0.001 gm uranium nitrate. Same on October 14, 15, 16, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29. On 30th 0.002 gm of same. Same on November 1, 2, and every third day until February 10. Killed May 12.

*Functional Test*—Twenty-five per cent of phenolsulphonephthalein given, excreted in one hour.

*Autopsy*—Excess of fluid in pericardial cavity, which was bulging. No edema elsewhere. Heart weight 5.75 gm. Kidneys, weight 11.55 gm, macro

scopically normal Microscopically scattered everywhere through the section and in many places surrounding a small collection of tubules, connective tissue is found in excess of normal and containing many lymphoid cells In these areas of connective tissue there are a few dilated tubules and an occasional dilated glomerular space

PROTOCOL 128—Rabbit Weight 1330 Caged November 16 On 17th given 0.005 gm uranium nitrate Repeated on December 8 Found dead December 20

Autopsy—No edema Lungs show consolidation Macroscopically other organs normal Kidney microscopically shows areas of round cell infiltration with some increase in connective tissue, little dilatation of tubules and glomerular spaces

PROTOCOL 129—Rabbit Weight 1520 Caged October 12 On 13th given 0.001 gm uranium nitrate Repeated October 14, 15, 16, 18, 19, 20, 21, 22, 23,

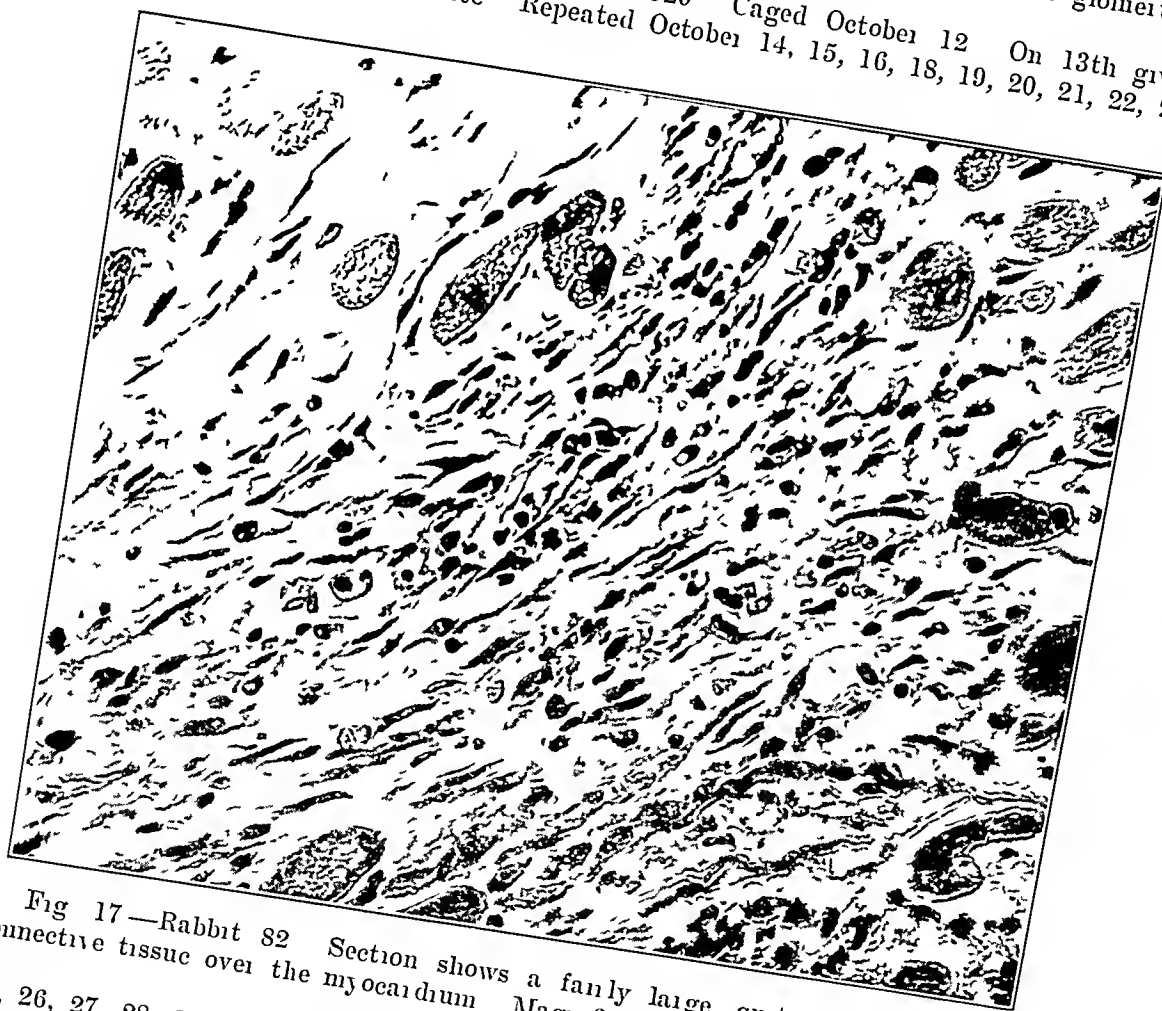


Fig 17—Rabbit 82 Section shows a fairly large, quite cellular area of connective tissue over the myocardium Magnification 185 diameters

25, 26, 27, 28, 29 On October 30 given 0.002 gm same, repeated every third day until February 10 Died April 7

Autopsy—No edema Heart weight 3.8 gm Kidneys, weight 7.2 gm, macroscopically show no change Microscopically there is an increase in connective tissue which entirely replaces the tubules in some places except for a few left in its midst Some of this connective tissue is fairly cellular In the areas of fibrous tissue there are some dilated tubules and occasional dilated glomerular spaces

PROTOCOL 130—Rabbit Weight 2000 Caged October 12 On 13th given 0.001 gm uranium nitrate Repeated October 14, 15, 16, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, and October 30 given 0.002 gm of same and repeated every third day until February 10 Killed March 24

*Autopsy*—No edema Heart weight 5 gm Kidneys weight 10.2 gm, cortex pale, microscopically there is very slight recent destruction of the tubules, in many areas there is connective tissue increase with dilatation of tubules and some glomerular spaces

PROTOCOL 177—Rabbit Weight 1250 Caged November 9 On 10th given 0.004 gm uranium nitrate Repeated December 2, 23, January 13, February 3, 24 Killed May 7

*Functional Test*—From 40 to 50 per cent of phenolsulphonephthalein excreted in one hour

*Autopsy*—No edema Heart weight 391 gm Kidneys, weight 11.75 gm, macroscopically normal, microscopically marked patchy and diffuse round cell infiltration, mostly in the cortex, but also in the medulla, many bands and patches of connective tissue often running in from the periphery and containing

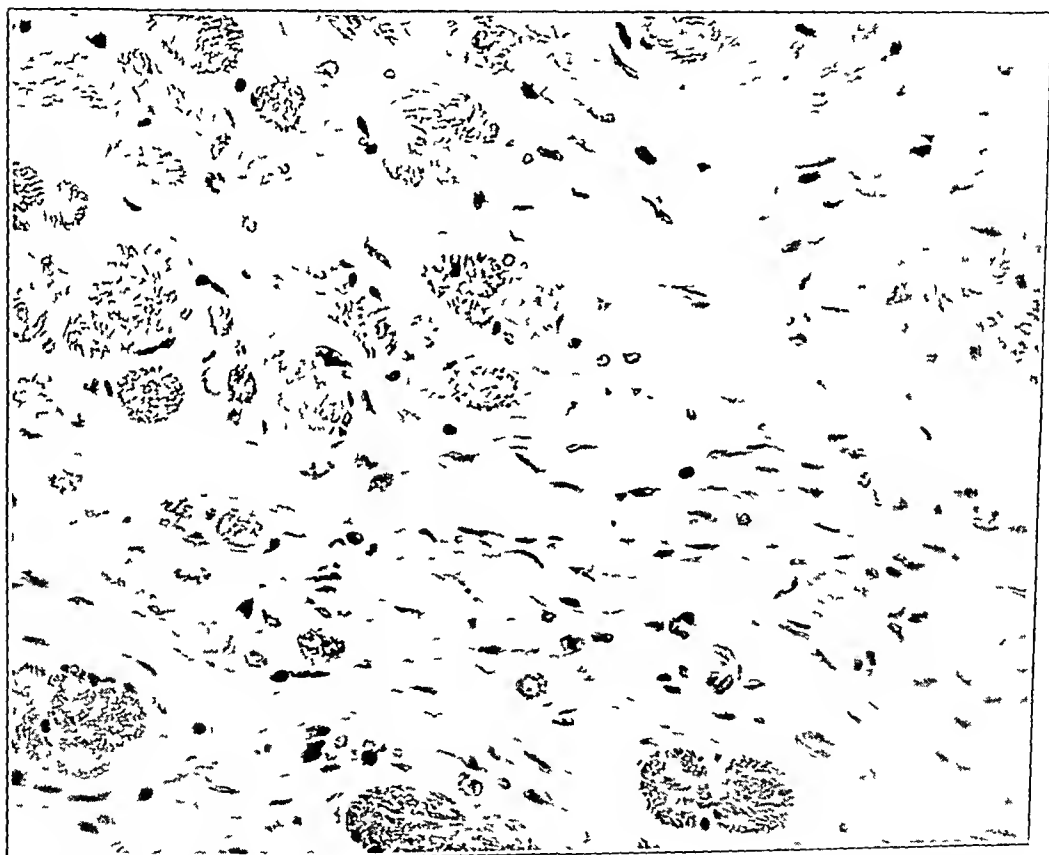


Fig 18—Rabbit 68 Section shows rather large focus of fairly dense connective tissue surrounding a small blood vessel and infiltrating between adjoining muscle fibers Magnification 185 diameters

dilated tubules in considerable numbers, some of the glomerular spaces are also greatly dilated

PROTOCOL 189—Rabbit Weight 1400 Caged November 16 On 17th given 0.005 gm uranium nitrate Repeated December 8, 31, January 20, February 14, March 11, 28 Killed April 27

*Functional Test*—Fifty per cent of phenolsulphonephthalein excreted in one hour

*Autopsy*—No edema Heart weight 55 gm Kidneys, weight 12.9 gm, macroscopically many white specks on surface microscopically marked increase in lymphoid cells scattered irregularly throughout the section and often very diffusely, some increase in connective tissue and a little dilatation of the tubules

PROTOCOL 190—Rabbit Weight 1390 Caged November 16 On 17th given 0.005 gm of uranium nitrate Repeated on December 9 and 31 Died January 11

*Autopsy*—No edema Heart weight 3.31 gm Kidneys, weight 12.85 gm, macroscopically large and soft, microscopically show rather diffuse connective tissue increase replacing tubules in some places, especially marked at junction of cortex and medulla, very little dilatation of tubules

PROTOCOL 192—Rabbit Weight 1470 Caged November 18 On 19th given 0.005 gm uranium nitrate Repeated December 11, January 3, 25, March 11, 28 and killed April 30

*Functional Test*—Slight delay in excretion of phenolsulphonephthalein

*Autopsy*—No edema Heart weight 3.4 gm Kidneys weight 8 gm Macroscopically normal Microscopically many small scattered patches of round cell infiltration, many bands of connective tissue running from the periphery and



Fig 19—Rabbit 273 Section shows normal pericardium with slight hemorrhagic exudation and congestion of subpericardial myocardium Magnification 185 diameters

patches scattered elsewhere in cortex In this there is also an infiltration of lymphoid cells and many dilated tubules

PROTOCOL 193—Rabbit Weight 2500 Caged November 18 On 19th given 0.005 gm uranium nitrate Repeated December 11, January 1, 23, February 17, March 11, 28 Died April 29

*Autopsy*—No edema Heart weight 8.4 gm Kidneys weight 14.9 gm Microscopically normal Microscopically, considerable round cell infiltration situated almost entirely in bands running in from the periphery In these areas much increase of connective tissue and sometimes in the medulla In the strips of connective tissue, often very extensive there is marked dilatation of the tubules—Some dilatation of tubules and glomeruli elsewhere



PROTOCOL 195—Rabbit Weight 1200 Caged November 18 On 19th given 0.005 gm uranium nitrate Repeated December 11, January 1, 23, February 14, March 11, killed on March 27

*Functional Test*—Fifty per cent of phenolsulphonephthalein excreted in one hour

*Autopsy*—No edema Heart weight 35 gm Kidneys, weight 12.1 gm, capsule strips easily, microscopically very marked round-cell infiltration in long bands running from the cortex and in scattered patches, very little connective tissue increase or dilatation of the tubules or glomeruli

PROTOCOL 196—Rabbit Weight 1200 Caged November 22 On 23d given 0.005 gm uranium nitrate Repeated December 16, January 6, 27, February 17, March 11, 28

*Functional Test*—Thirty per cent of phenolsulphonephthalein excreted in one hour

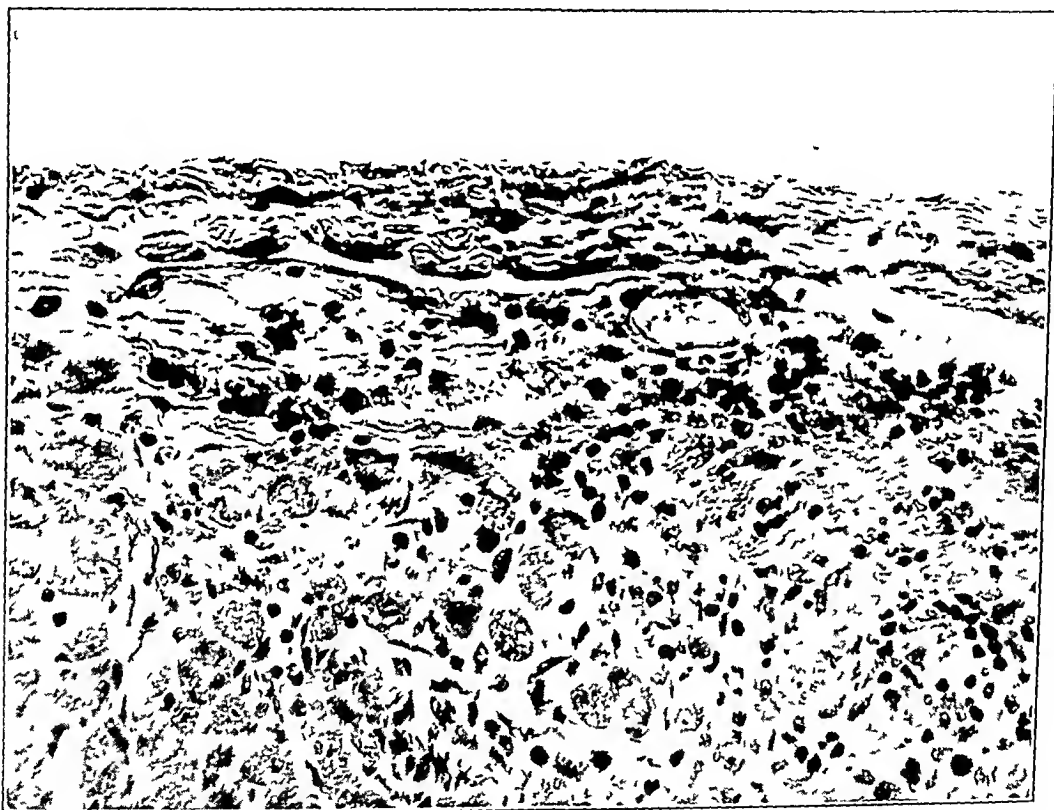


Fig 20—Rabbit 279 Section shows thickening of pericardium with increased cellularity of pericardium and myocardium Magnification 185 diameters

*Autopsy*—No edema Heart weight 45 gm Kidneys, weight 13 gm On section cortex very pale Microscopically scattered throughout the section there are a few small patches of lymphoid cells Great amount of connective tissue formation, entirely replacing the tubules in some portions of the cortex In the connective tissue usually near the periphery but also present in the deeper portions are many dilated glomerular spaces

PROTOCOL 207—Rabbit Weight 1530 Caged December 2 On 3d given 0.005 gm uranium nitrate Repeated every third day until March 28 Killed April 28

*Functional Test*—Sixty per cent of phenolsulphonephthalein excreted in one hour



*Autopsy*—No edema Heart weight 42 gm Kidneys, weight 96 gm, cortex strips easily, very pale on section, otherwise normal Microscopically the capsule and cortex beneath is very irregular in outline with some connective tissue increase often running in from the depressions, some round cell infiltration in the newly-formed connective tissue and in small patches elsewhere, some dilatation of the tubules and glomeruli, especially the latter

PROTOCOL 208—Rabbit Weight 1740 Caged December 2 On 3d given 0.005 gm uranium nitrate Repeated every third day until March 28 Killed April 28

*Functional Test*—Very slight excretion of phenolsulphonephthalein in one hour, too small to estimate

*Autopsy*—Excess of fluid in all body cavities Heart weight 642 gm Kidneys, weight 1195 gm, macroscopically normal, capsule strips easily Micro-



Fig 21—Rabbit 208 Section shows slight thickening of pericardium with slight edema and congestion of vessels of pericardium and myocardium Magnification 185 diameters

scopically very little round cell infiltration, but marked increase of connective tissue Some portions of the section show no tubules, the whole field being made up of connective tissue Frequently small islands of tubules may be seen in the mass of surrounding tissue Scattered diffusely through the organ are some slightly dilated tubules

PROTOCOL 221—Rabbit Weight 1460 Caged December 2 On 3d given 0.005 gm uranium nitrate Repeated every third day until March 21 Killed March 24

*Autopsy*—No edema Heart weight 44 gm Kidneys, weight 116 gm macroscopically appear normal microscopically show patches of infiltration

with round cells and areas of increase in connective tissue. There is considerable dilatation of the tubules in groups or bands and some glomerular spaces are also much increased in size.

PROTOCOL 225—Rabbit Weight 1700 Caged December 6 On 7th given 21 minims 1 per cent solution potassium bichromate Repeated December 31, January 22, February 10, March 3 Killed March 24

*Autopsy*—Slight amount of straw colored fluid in the abdominal cavity, none in thoracic cavity Heart weight 57 gm Kidneys, weight 125 gm, macroscopically normal, except for small depressions on the surface, microscopically there are small strips of connective tissue running in from the depressions on the surface, in which there is considerable round cell infiltration. No dilatation of the tubules or glomeruli.

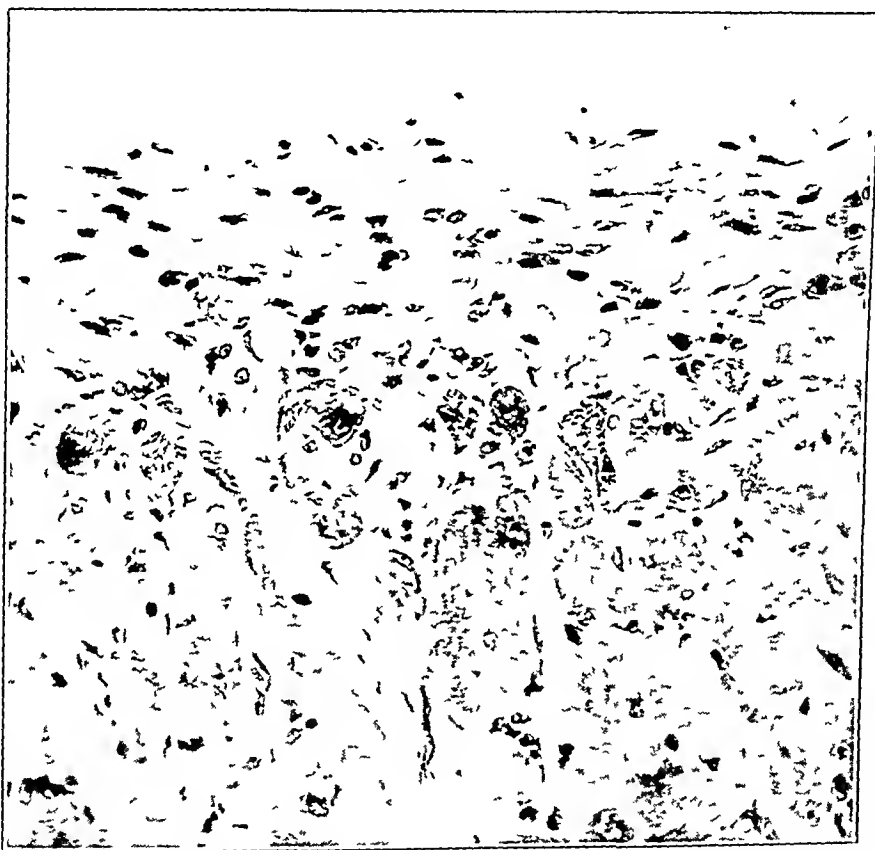


Fig 22—Rabbit 270 Section shows slight thickening of peritubular interstitium with increased cellularity of peritubular interstitium and myometrium Magnification 185 diameters

PROTOCOL 226—Rabbit Weight 1310 Caged December 6 On 7th given 0.002 gm uranium nitrate Repeated December 11, 23, 31, January 3, 6, 10 Found dead January 12

*Autopsy*—Kidneys microscopically, considerable increase in connective tissue with consequent disappearance of tubules. Some of the connective tissue is fairly cellular, other portions much less so. There are a few patches of dilated tubules.

PROTOCOL 233—Rabbit Weight 1600 Caged December 16 On 17th given 8 minims Fowler's solution subcutaneously Repeated December 23, January 3, 10, 17, 25, February 3, 14, 24, March 12 Killed April 28

*Functional Test*—From 60 to 90 per cent phenolsulphonephthalein excreted in one hour

*Autopsy*—No edema Heart weight 5.3 gm Kidneys, microscopically are normal, except for congestion of glomeruli and some increase in cellular elements

PROTOCOL 238—Rabbit Weight 1730 Caged December 16 On 17th given 8 minims Fowler's solution by stomach tube Repeated December 23, January 3, 10, 17, 25, February 3, 14, 24, March 12, killed May 12

*Functional Test*—Sixty per cent phenolsulphonephthalein excreted in one hour

*Autopsy*—No edema Heart weight 5.55 gm Kidneys, weight 11.15 gm, macroscopically show a few pinpoint hemorrhagic spots with slight depressions Microscopically a few small patches of round cell infiltration Glomeruli very much congested with some increase in the cells

PROTOCOL 243—Rabbit Weight 2280 Caged January 1 On 3d given 10 minims Fowler's solution subcutaneously Repeated on 10th and 17th Found dead on 19th

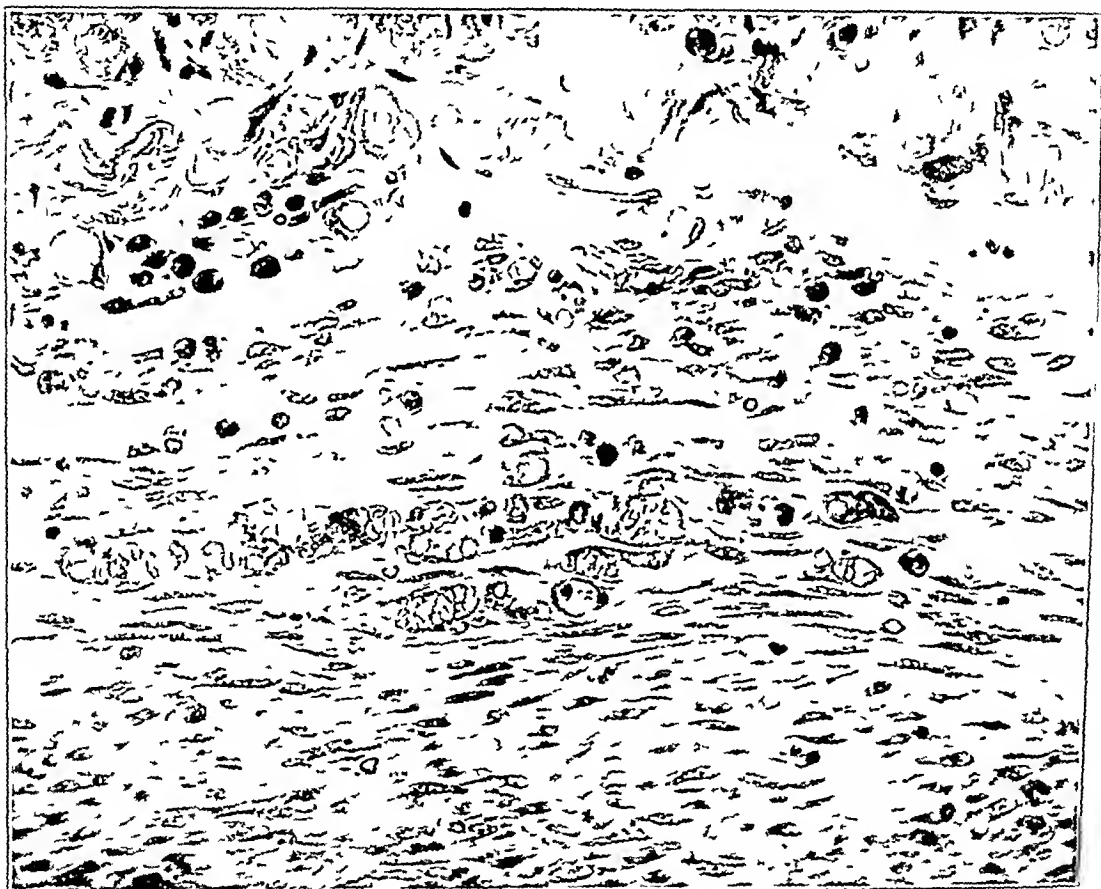


Fig 23—Rabbit 79 Section shows at one side few fibers of the upper layer of the myocardium Rest of section composed of very much thickened, cellular vascular pericardium Magnification 185 diameters

*Autopsy*—No edema Heart weight 7.3 gm Kidneys, weight 16.9 gm, capsule strips easily On section pinpoint hemorrhagic spots seen in cortex Microscopically the glomeruli are much congested and upper larger than normal, because vessels are full of blood Otherwise normal

PROTOCOL 245—Rabbit Weight 2050 Caged January 3 On 4th given 0.0125 gm potassium bichromate Repeated January 25 Feb 10, March 3 Died March 11

*Autopsy*—No edema Microscopically the kidneys show the characteristic increase in connective tissue situated for the most part near the periphery and

often entirely replacing the tubular structure. There are also a few dilated tubules.

**PROTOCOL 257**—Rabbit. Weight 2330. Caged January 7. On 8th given 21 mms potassium bichromate, 1 per cent. Repeated on 27, February 10, March 3. Found dead April 13.

**Autopsy**—No edema. Slight acute fibrinous pericarditis. Heart weight 6.35 gm. Kidneys, weight 10.8 gm, macroscopically capsule strips easily, surface very irregular with many deep depressions. On section bands of connective tissue can be seen running down from the depression into the substance of organ. Microscopically in the areas beneath the depressions are bands of connective tissue which have almost entirely replaced the tubules, though the glomeruli still remain. There is some increase in lymphoid cells, but no dilatation of tubules.

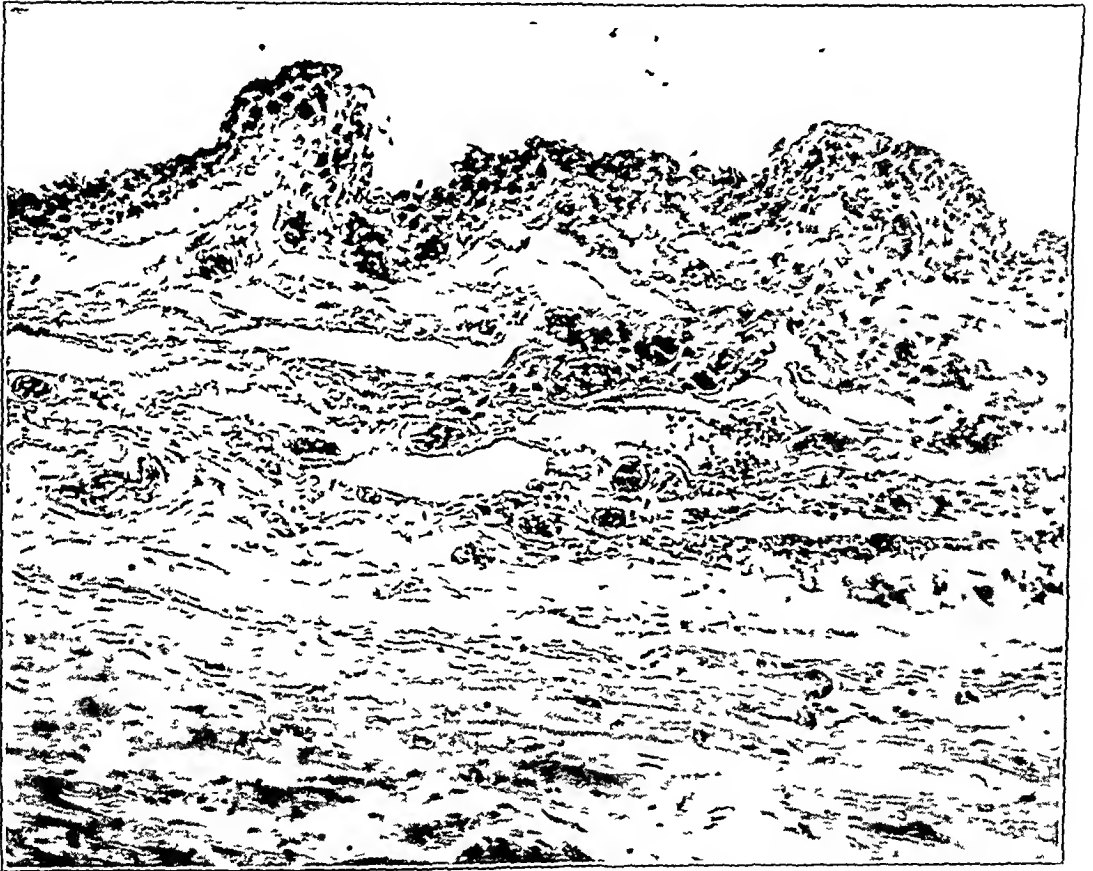


Fig 24—Rabbit 266. Section shows much thickened cellular vascular pericardium with papular surface. Magnification 100 diameters.

**PROTOCOL 264**—Rabbit. Weight 2100. Caged January 31. February 13 given 0.002 gm uranium nitrate. Repeated every three days up to March 28. Killed April 30.

**Functional Test**—Twenty-four per cent of phenolsulphonephthalein excreted in one hour.

**Autopsy**—Slight amount of free fluid in all cavities. Heart weight 4.3 gm. Kidneys, weight 12 gm, macroscopically normal. Capsule strips easily. Some small areas of round cell infiltration scattered through this section. Very marked increase in the connective tissue, often in long bands running from periphery down into medulla or scattered in smaller areas irregularly through the cortex. In the connective tissue there are a few moderately dilated tubules.

## STUDY VI STUDY OF THE WEIGHTS OF KIDNEYS AND HEARTS IN NORMAL RABBITS AND IN THOSE WITH EXPERIMENTAL CHRONIC NEPHRITIS

R. M. SMITH, M.D., BOSTON

In the course of the study of animals with experimental nephritis it has been possible to collect a considerable amount of material concerning the comparative weights of the heart and kidneys in rabbits. There were available also in the laboratory many data on normal rabbits, which served as a standard of weights. The observations seem sufficiently interesting to record.

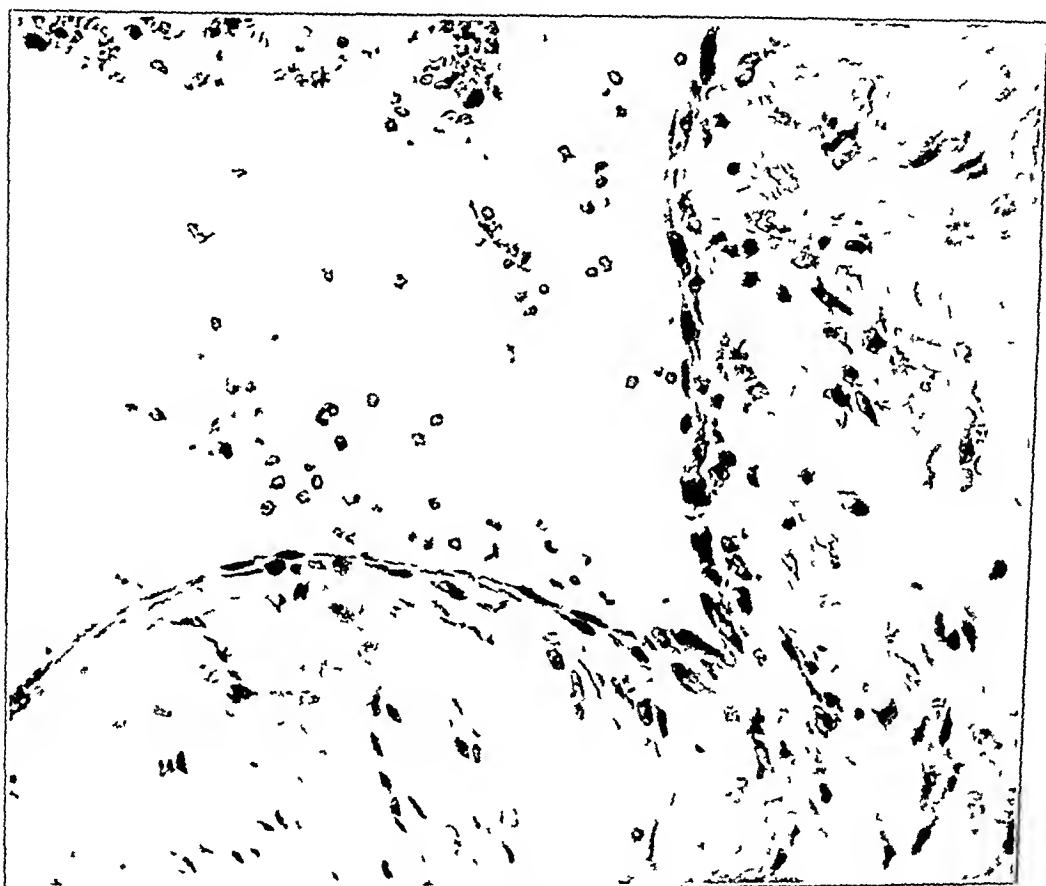


Fig. 25—Rabbit 268. Section shows a portion of myocardium with overlying endocardium. Endocardium shows proliferation of the endothelial cells with slight edema of the endocardial layer. Magnification 185 diameters.

Grober<sup>5</sup> reports from a study of cardiac hypertrophy in relation to exercise that in caged rabbits the proportion of the body-weight to the weight of the heart is as 1 is to 0.0024. This figure corresponds very closely with that of our normal rabbits, therefore it is taken as the

<sup>5</sup> This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

<sup>6</sup> Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D. C.

<sup>7</sup> 5. Grober. Untersuchungen zur Arbeitshypertrophie des Herzens. Deutsch. Arch. f. klin. Med. 1907, xci, 502.

standard. No figures could be found in regard to the ratio of body-weight to the weight of the kidneys—our own weights vary considerably—but the great majority are between 1 to 0.0055 and 0.0075, the average of twenty-five rabbits was 0.0066. This makes the relation of the weight of the heart to the weight of the kidneys as 1 is to 2.75.

In some instances it was somewhat difficult to determine the exact weight of the animals. Often during experimentation an animal lost weight markedly, so that at the time of death its body weight was obviously less than it should be. Also, some of the female rabbits were pregnant, and this of course increased their weight. In most instances the weight of the animal at the beginning of the experiment was taken as the correct body-weight. Only marked variations from the normal in heart and kidneys were considered as pathological. If the weights seemed somewhat abnormal but the proportion of heart to kidney was not disturbed no account was made of the variations.

TABLE 1.—TWENTY-FIVE NORMAL RABBITS

No	Wt of Animal	Wt of Heart	Wt of Kidneys	Wt of Animal to Wt of Heart as 1 is to	Wt of Animal to Wt of Kidneys as 1 is to	Wt of Heart to Wt of Kidneys as 1 is to
1	1320	3.2	9.67	0.0242	0.0732	
2	1310	3.3	9.75	0.0252	0.0744	
3	1300	3.1	9.7	0.0238	0.0746	
4	1290	2.94	8.64	0.0228	0.0670	
5	1380	3.15	10.5	0.0228	0.0760	
6	1335	2.5	9.0	0.0187	0.0674	
7	1350	2.8	8.4	0.0207	0.0622	
8	1350	2.95	7.74	0.0218	0.0573	
9	1365	4.84	8.75	0.0354	0.0641	
10	1320	2.52	9.44	0.0190	0.0715	
11	1250	2.3	6.7	0.0184	0.0536	
12	1175	2.25	6.9	0.0191	0.0587	
13	1130	2.8	8.4	0.0247	0.0743	
14	1120	2.7	8.2	0.0241	0.0732	
15	1180	2.3	7.3	0.0194	0.0610	
16	1070	2.87	8.5	0.0268	0.0794	
17	1150	2.3	8.1	0.0200	0.0704	
18	1410	3.35	9.35	0.0237	0.0677	
19	1120	3.9	8.7	0.0348	0.0777	
20	1270	3.4	7.6	0.0267	0.0600	
21	1300	3.4	6.4	0.0261	0.0492	
22	1240	3.6	6.9	0.0290	0.0536	
23	1250	2.9	7.5	0.0232	0.0600	
24	1400	4	9.75	0.0285	0.0696	
25	2200	6.4	15.2	0.0294	0.0691	
Average				0.024	0.066	2.75

A study of the kidney sections from the organs whose weight showed a variation from the normal did not establish any definite basis for this change. The same was true of those animals in which there was cardiac hypertrophy. These animals showed no greater round-cell infiltration,

connective tissue formation or dilatation of tubules of the kidney than those of the same groups with normal weights

TABLE 2—URANIUM SLRILS

No	Wt of Animal	Wt of Heart	Wt of Kidneys	Wt of Animal to Wt of Heart as 1 is to	Wt of Animal to Wt of Kidneys as 1 is to	Wt of Heart to Wt of Kidneys as 1 is to
130	2250	5	10.2	00222	0045	2.04
221	1460	4.4	11.6	0030	0080	2.63
189	1400	5.5	12.9	0039	0090	2.34
195	1200	3.5	12.1	0029	010	3.45
207	1530	4.2	9.6	00261	00626	2.28
192	1470	3.4	8	00231	00544	2.35
264	2100	4.3	12	00204	00571	2.79
196	1200	4.5	13	00375	0108	2.88
194	1300	3.5	10	0027	0076	2.85
247	1430	4.6	11.7	0032	0081	2.54
261	1760	4.3	10.8	0024	0061	2.51
227	1350	3.6	8.1	0026	006	2.25
252	2500	6.6	15.7	0026	0062	2.38
197	1200	3.7	8.3	0030	0069	2.24
250	2400	5.8	12.7	0024	0053	2.17
124	1870	5.75	11.55	00306	0061	2.00
129	1520	3.8	7.2	0025	0047	1.89
208	1740	6.42	11.95	0037	0069	1.89
209		5.65	11.00			1.94
260	1575	4.65	7.75	0029	0049	1.66
190	1390	3.31	12.85	0023	0092	3.89
249	2080	5.1	11.5	0024	0056	2.25
248	1720	4.2	9.52	0024	0055	2.26
177	1250	3.91	11.75	0031	0094	3.0
178	1580	4.8	11.8	0030	0074	2.46
187	1360	2.9	7.2	0021	0053	2.47
193	2500	8.4	14.9	0033	0059	1.77

TABLE 3—CHROMIUM SLRILS

No	Wt of Animal	Wt of Heart	Wt of Kidneys	Wt of Animal to Wt of Heart as 1 is to	Wt of Animal to Wt of Kidneys as 1 is to	Wt of Heart to Wt of Kidneys as 1 is to
134	1850	4.1	12.9	0022	007	3.14
135	1900	5.0	8.7	0026	0046	1.74
231	1330	4	10.8	003	0081	2.7
244	2400	5.7	14.8	0023	0061	2.6
263	2000	3.9	9.1	0019	0045	2.33
262	1550	9.5	14.8	0029	0095	3.29
257	2330	6.35	10.8	00272	00463	1.70
222	1300	6.1	17	0047	013	2.78
223	1530	4.7	11.7	0030	0076	2.49
224	1730	5	14.5	0028	0083	2.90
225	1700	5.7	12.5	0033	0073	2.15
258	3310	8.7	16	0026	0048	1.83
228	1310	4.3	12.8	0032	0097	2.97

The study of the charts however, shows some interesting facts. Of the animals having lesions produced by uranium nitrate and potassium bichromate taken together 39.4 per cent showed some variations from normal of the weights of heart and kidneys. The smallest percentage was

in those having uranium nitrate in large doses every three weeks, but histologically, they showed as a group very marked lesions. Over one-half of those showing variations, eight in number, or 21.5 per cent, showed a small kidney, one-half of them associated with cardiac hypertrophy.

TABLE 4—FOWLER'S SOLUTION SERIES

No	Wt of Animal	Wt of Heart	Wt of Kidneys	Wt of Animal to Wt of Heart as 1 is to	Wt of Animal to Wt of Kidneys as 1 is to	Wt of Heart to Wt of Kidneys as 1 is to
237	1950	5.8	14.5	003	0073	2.50
236	1920	5.35	17.2	0027	009	3.21
235	2500	6.8	18.7	0027	0075	2.75
239	2250	5.1	14.6	0022	0065	2.86
243	2280	7.3	16.9	0032	0074	2.31
234	2470	4.86	11.9	0019	0048	2.45
238	1730	5.55	11.15	0032	0064	2
253	2250	5.5	11	0024	0049	2
255	2180	5.1	15.8	0023	0072	3
254	1950	5.15	12.1	0026	0062	2.26

TABLE 5—ANIMALS RUNNING OVER 3 MONTHS

	No with Wts Recorded	Variation in Weights	Small Kidneys Normal Heart	Normal Kidneys Large Heart	Small Kidneys Large Heart	Large Kidneys
Uran 0.002 gm every 3 days	11	6=54.5%	2	2	2	0
Uran 0.005 gm every 3 weeks	15	3=20%	0	0	1	2
Pot Bichrom 0.0125 gm every 3 weeks	12	6=50%	2	1	1	2
Uran and Bichrom together		15	4	3	4	4
	38	39.4%	10.5%	7.9%	10.5%	10.5%
Fowler's sol 8.10 in every 3 weeks	8	4=50%	1	1	0	2
Total	46	19	5	4	4	6

TABLE 6—FUNCTION AND EDEMA TESTS IN ANIMALS WITH ABNORMAL WEIGHTS

	No	Functional Test Tied	Functional Test Delay	Edema Test Tied	Edema Test Present
Animal with small kidney, normal heart	5	3	3	5	0
Normal kidney, large heart	4	3	2	4	3
Small kidney, large heart	4	2	1	5	2
Large kidney	6	5	1	5	0

The animals with small kidneys and normal hearts in which the functional test was tried, all showed delayed excretion, but none of them had edema. Three out of four of those with heart hypertrophy in addition showed edema. Those with large kidneys showed, with one exception, normal excretion and no edema.

Further observations in a larger number of animals are necessary before definite conclusions can be drawn.



STUDY VII PRODUCTION OF EDEMA IN EXPERIMENTAL CHRONIC NEPHRITIS

R. M. SMITH, M.D., BOSTON

Among the problems connected with the study of experimental nephritis, is the question of the formation of edema and the relation, if any, which it bears to the renal lesion. There seems to be a rather general belief, supported by certain experimental work, that injury to the tubules



Fig. 26—Rabbit 279. Section shows portion of endocardium with moderate cellular infiltration. Myocardium shows cellular infiltration. Magnification 185 diameters.

of the kidney alone will not cause edema, but that there must be in addition some lesion of the vascular system. What part sodium chloride plays in the production of edema has also been studied by many investi-

\*This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

\*Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D. C.

gators. In acute nephritis, produced by mercuric nitrate and rarely by potassium bichromate, edema occurs without the addition of salt to the diet or without the administration of both salt and water in excess. This does not occur, however, in chronic nephritis in rabbits, except very rarely, and not at all in the series of animals in this laboratory.

The following experiment was carried out to see if any further light could be thrown on this subject. All the animals used for experiment had received toxic substances extending over a period in excess of three months, most of them had had no injections for several weeks and thus did not have an acute lesion. A detailed description of the production of the lesion together with the macroscopic and microscopic appearance of

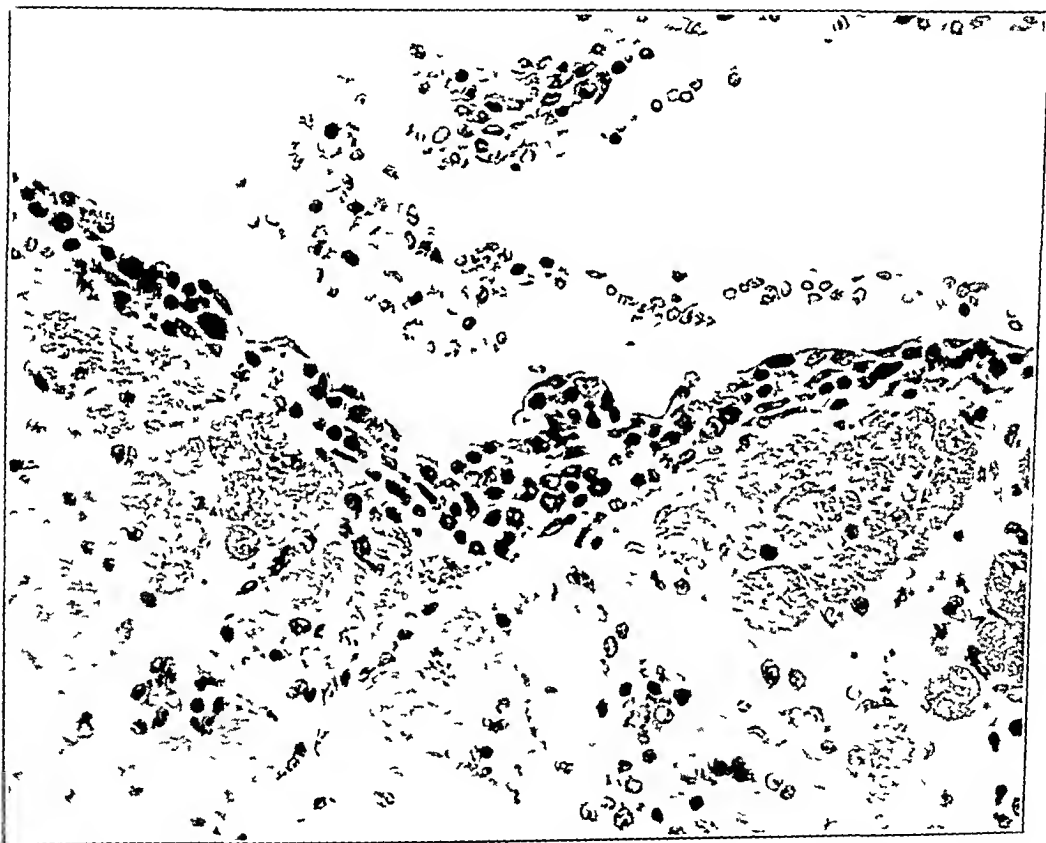


Fig. 27—Rabbit 79. Section shows quite cellular endocardium with moderately cellular underlying myocardium. Magnification 185 diameters.

the kidneys will be found in another paper. The animals were given 100 c.c. of a 3 per cent sodium chloride solution by stomach-tube daily for a period of from four to six days and then killed. Thirty-five animals were thus treated and at autopsy nine showed edema of varying degrees.

The animals used for experimentation had lesions produced as follows:

Uranium Nitrate 0.002 gm. every third day	= 8
Uranium Nitrate 0.005 gm. every three weeks	= 11
Potassium Bichromate 0.0125 gm. every three weeks	= 10
Fowler's solution 8.10 m. every three weeks	= 6
	—
	35

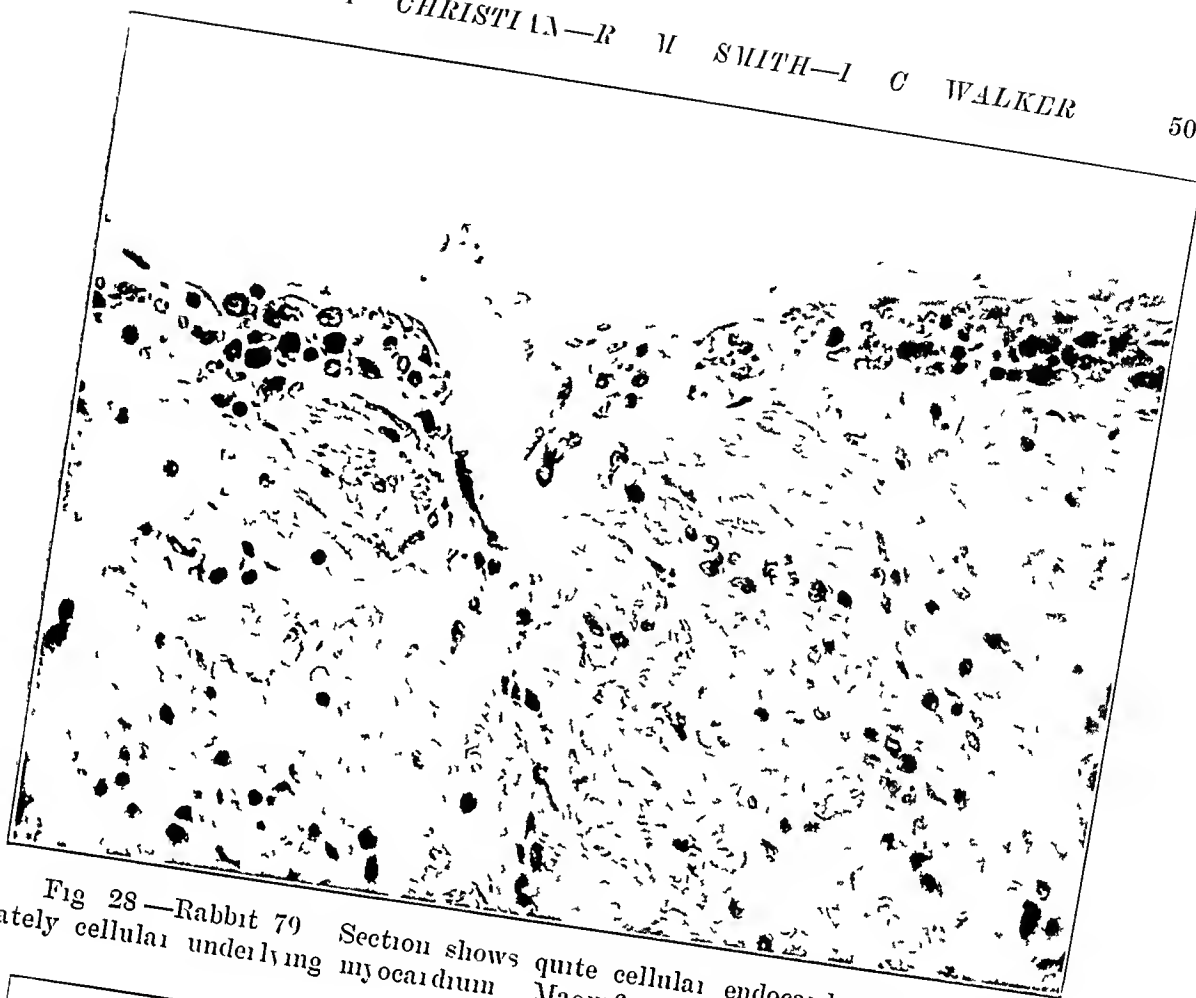


Fig 28—Rabbit 79 Section shows quite cellular endocardium with moderately cellular underlying myocardium Magnification 185 diameters

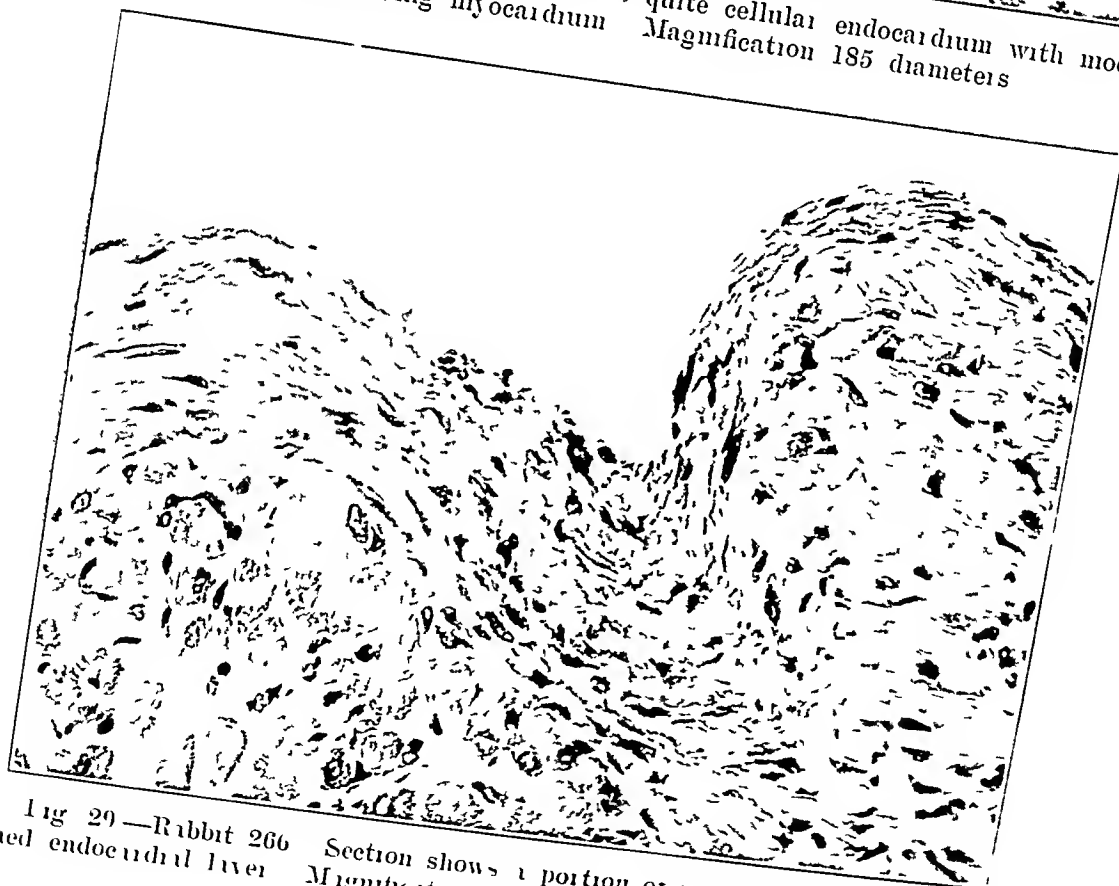


Fig 29—Rabbit 266 Section shows a portion of myocardium with a thickened endocardial layer Magnification 185 diameters

The nine showing edema were thus distributed

Uranium Nitrate 0.002 gm every third day	= 6
Uranium Nitrate 0.005 gm every three weeks	= 2
Potassium Bichromate 0.0125 gm every three weeks	= 1
	—
	9

Histologically the kidneys of the animals showing edema were not different from those of the same group in which no edema developed. The lesions were of the same character and of no greater or no less degree.

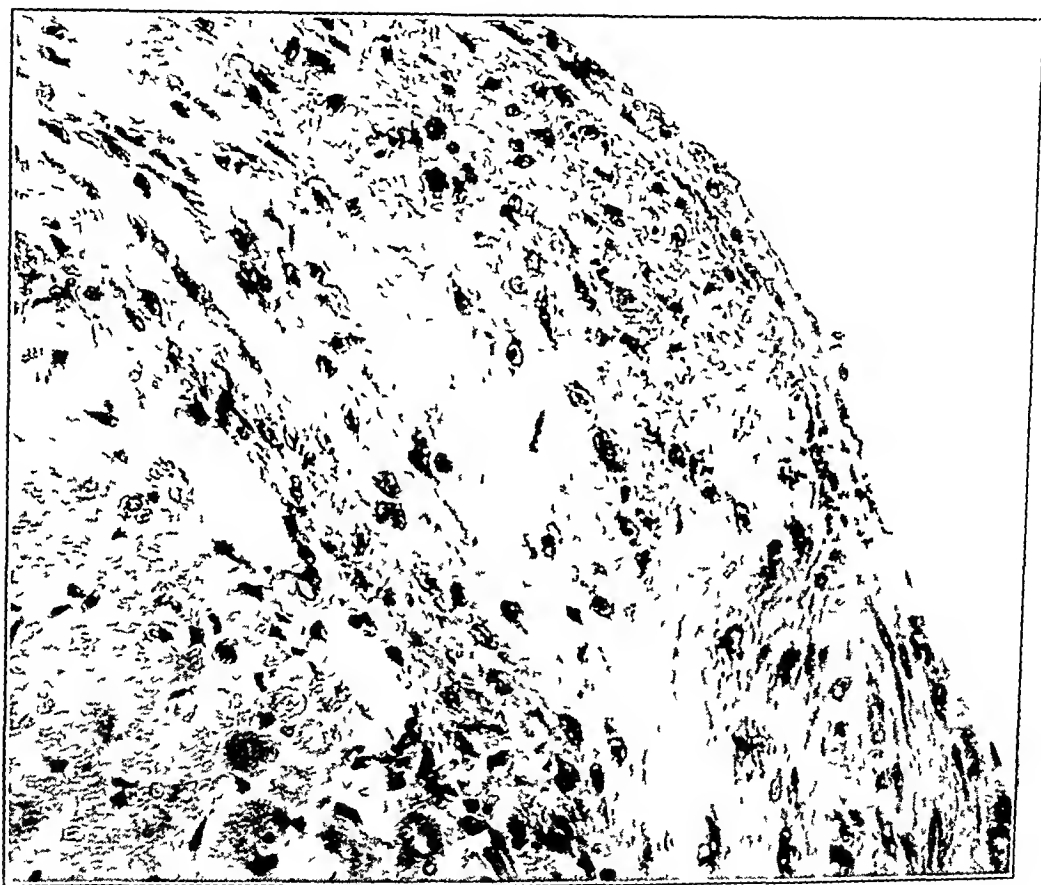


Fig. 30.—Rabbit 266. Section shows a small bit of the myocardium with a very much thickened, somewhat cellular endocardium. Magnification 185 diameters.

It seems then that the cause of the edema must be sought elsewhere than in histological variations from the normal.

The animals were weighed at the beginning of the experiment and each day after that before the salt solution was given. Of those not showing edema at autopsy, twenty-six in number, there was a gain in weight in twelve, a loss of weight in nine, no change of weight in five.

In those showing edema at autopsy, nine in all, there was a gain in weight in four, a loss of weight in four, no change of weight in one.

Therefore, a weight chart is no indication of the appearance of edema in rabbits experimented on in this way

In the first animals used the daily amount of urine excreted was measured, but no constant or marked variation in the output could be found and the procedure was therefore given up as being of no value in this connection

These same animals were also subjected to the functional test with phenolsulphonephthalein. Though this matter is reported in another paper the results are interesting from this different point of view. Of the eight animals having uranium 0.002 gm every third day, and showing

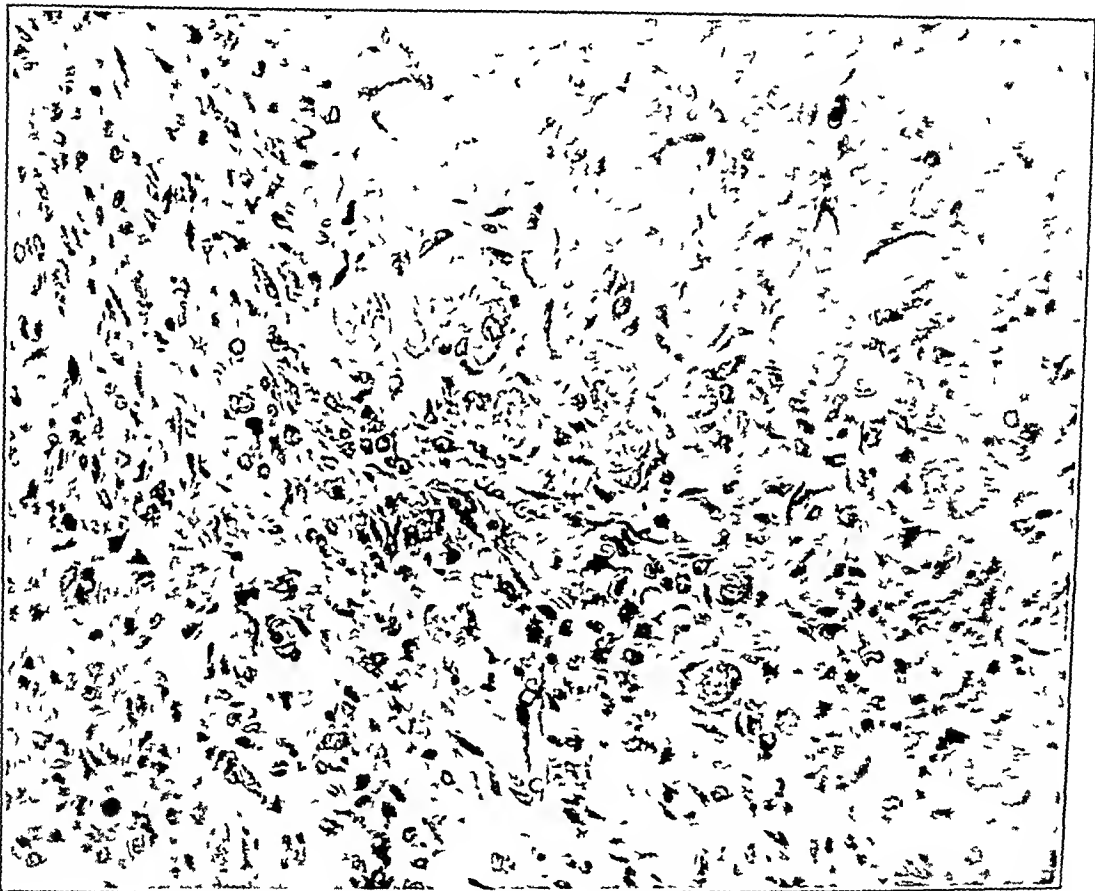


Fig 31—Rabbit 266. Section shows a portion of myocardium very largely replaced by cellular connective tissue. This connective tissue was continuous with the connective tissue of the endocardium.

edema, five were tested with phenolsulphonephthalein, and four showed delayed excretion. Of the animals having uranium nitrate 0.005 gm every three weeks and showing edema, two in number the test was tried in one and the excretion was normal. The test was not tried in the rabbit having edema with a bichromate lesion. This would perhaps indicate a functional injury to the kidney cells which would not allow the normal excretion of either water or some other substance. The relative weight of heart and kidney to the body-weight is also interesting in this connec-

tion Of the first maximum group of animals showing edema six in number, two had small kidneys, four had enlarged hearts

In the second maximum group, two in number the heart and kidney weights were normal The one animal with edema in the bichromate series had an enlarged heart The number of animals here is too small for any definite conclusions, but it is suggestive that of the nine animals having edema, five had cardiac hypertrophy and only two, small kidneys

These facts are collected in Table 7

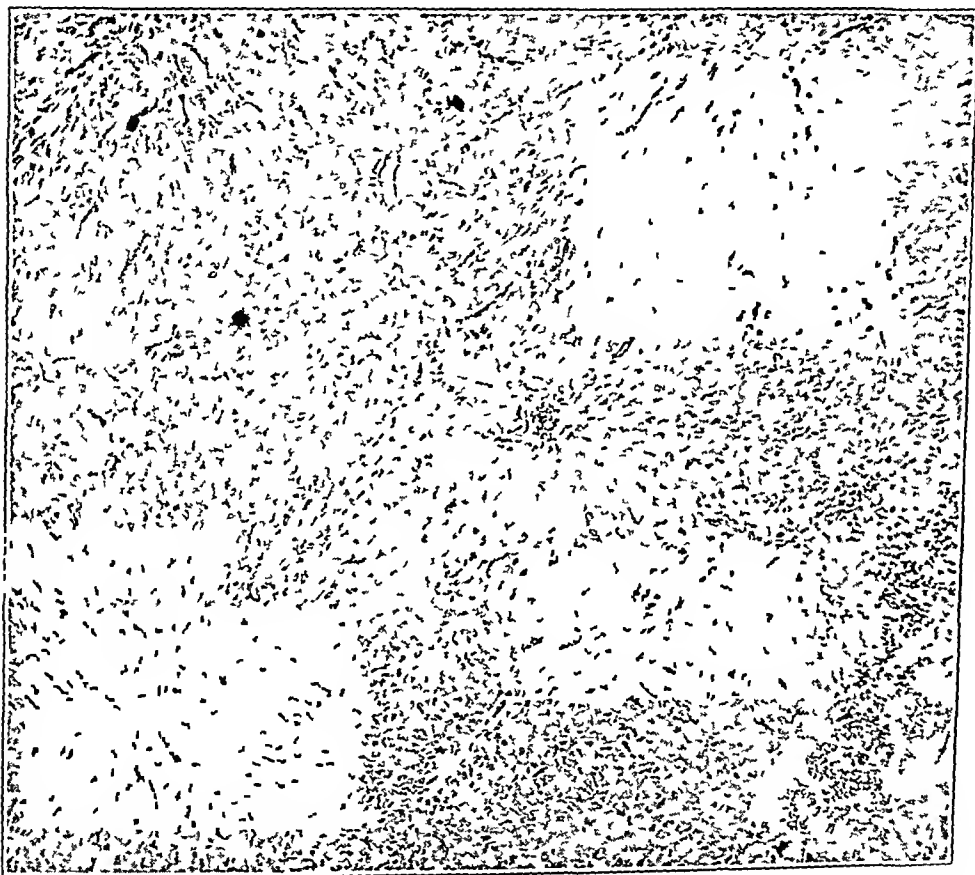


Fig 32—Rabbit 273 Liver shows acute congestion of the sinusoids Magnification 125 diameters

TABLE 7—EDEMA EXPERIMENTS

	Test Tried	Edema Present	Phenol sul- fate Test Tried	Excre- tion Delayed	Small Kidney	Large Heart
Uran 0.002 gm every 3 days	8	6	5	4	2	4
Uran 0.005 gm every 3 wks	11	2	1	0	0	0
Bichrom 0.0125 gm every 3 wks	10	1	0		0	1
Fowler's 8-10 m every 3 wks	6	0				
Total	35	9	6	4	2	5

From these experiments we may draw the following conclusions

1 Edema may be produced in animals having experimental chronic kidney lesions by the administration of sodium chlorid and water

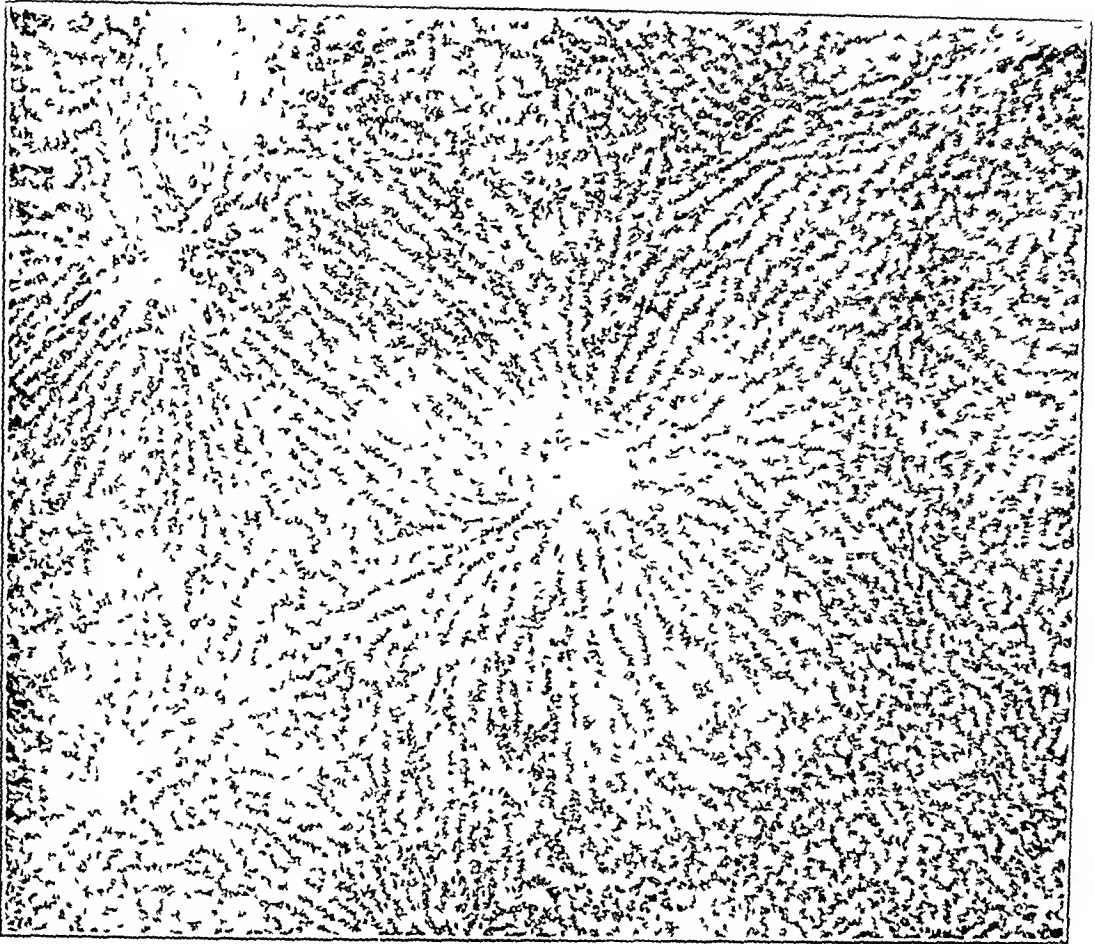


Fig 33—Rabbit 266 Liver shows distinct dilatation of the sinusoids, particularly those radiating out from the central vein in the center of the picture with atrophy of the hepatic cells. Magnification 125 diameters.



Fig 34—Rabbit 282 Liver shows fairly marked dilatation and congestion of the sinusoids. Magnification 125 diameters.



2 The occurrence of edema does not appear to bear any direct relation to the severity or character of the lesion of the kidney as shown by histological study

3 The weight of the animals during experimentation does not serve as a reliable guide for the appearance or non-appearance of edema

4 The amount of urine excreted gives no aid in the study of edema formation

5 Functional tests in animals showing edema would suggest the possibility of some damage to excretory function of cells

This matter requires further study

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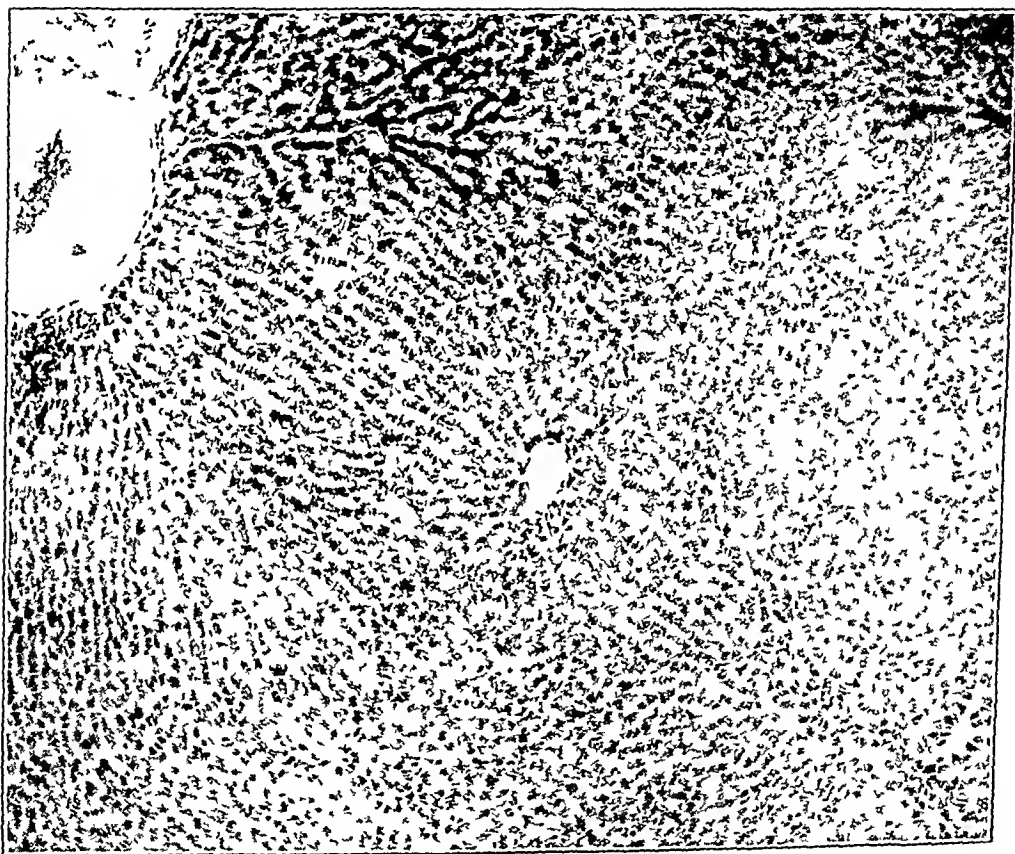


Fig 35—Rabbit 268 Liver shows very slight change and may be taken as a fairly normal liver Magnification 125 diameters

#### STUDY VIII A RENAL FUNCTION TEST (PHENOLSULPHONEPHTHALEIN) IN ANIMALS WITH EXPERIMENTAL CHRONIC NEPHRITIS

R M SMITH, M D, BOSTON

There have been many tests devised to investigate the excretory function of the kidney The basis of most of them is the time required to

\*This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases

\*Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910 Washington, D C



excrete a certain portion or all of a measured amount of a given drug. The most recently tried drug is phenolsulphonephthalein. It has been used by Rowntree and Geaghty<sup>6</sup> to test the excretory power of kidneys in human beings. They say in favor of this drug that it is all excreted by the kidney, that the drug undergoes no chemical change in the body, and that it is excreted quickly. It is stated that 40 to 60 per cent of the amount given is excreted in normal individuals within one hour after it first appears in the urine.

Experiments were tried with this drug in animals having chronic kidney lesions produced by injection of uranium nitrate, potassium

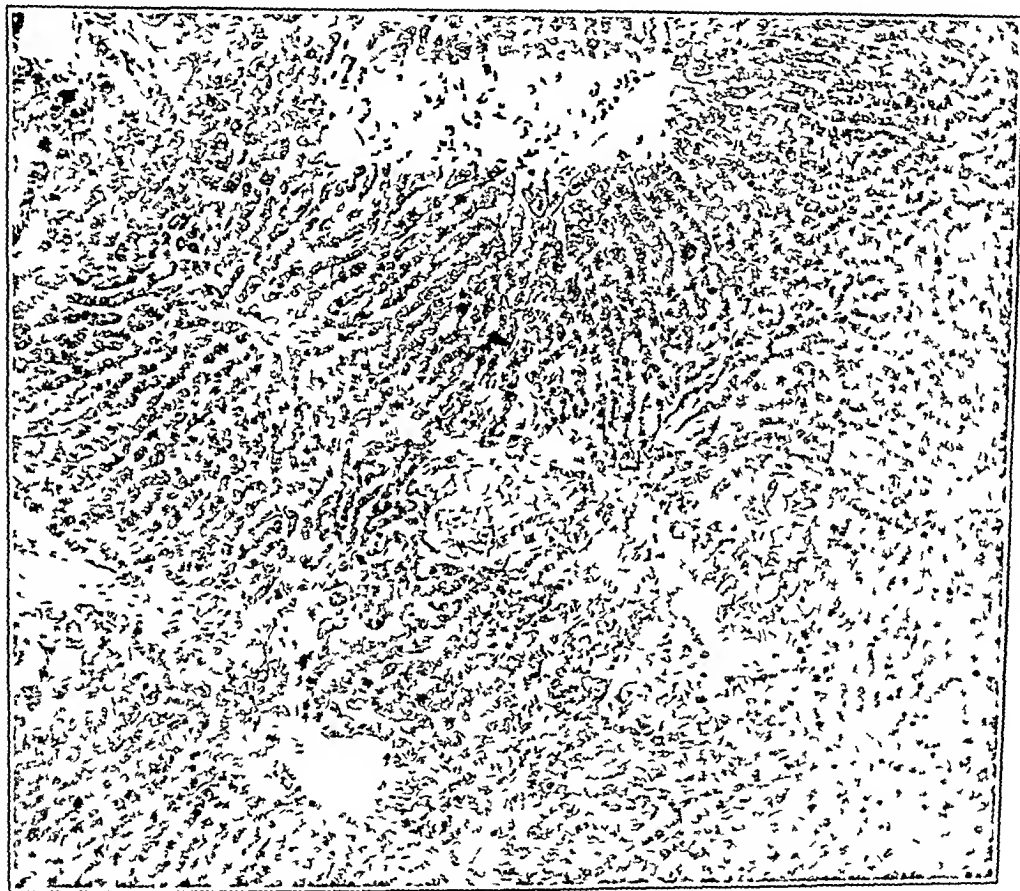


Fig. 36.—Rabbit 79. Liver shows irregular areas of almost complete disappearance of liver cells and their place taken by very large dilated sinusoids or lakes of blood. Magnification 125 diameters.

bichromate and arsenic. The details of the production of the lesion have been described fully in another paper. The functional tests were carried on in the following manner:

One milligram of phenolsulphonephthalein in watery solution was injected subcutaneously. Male rabbits were used at first so that catheterization was easy. They were catheterized immediately following the injection.

<sup>6</sup> Rowntree and Geaghty. *Jour. Pharm. and Exper. Therap.* 1909-1910, 1, 579.

tion, and the urine was allowed to flow into a bottle which contained a few drops of strong sodium hydrate solution. As soon as any of the drug appeared in the urine it could be detected by the pink color which it is well known alkaline solutions of phenolsulphonephthalein assume. The time was then recorded and the catheter withdrawn. At the end of one hour the catheter was again inserted and all the urine in the bladder collected. The bladder was then washed out once with water and the wash-water added to the collected urine. This was then made strongly alkaline with sodium hydrate, and diluted to 50 cc with water. This of course gave a solution with a depth of color dependent on the amount



Fig 37—Rabbit 79. Liver shows irregular areas of almost complete disappearance of liver cells and their place taken by very large dilated sinusoids or lakes of blood. Magnification 125 diameters.

of phenolsulphonephthalein it contained. To determine the amount of this a standard solution of phenolsulphonephthalein was prepared containing a measured amount in 50 cc of fluid (water and urine). For a portion of the diluent of the standard solution urine was used, otherwise the colors were not exactly the same in the control and the test as the solution to be tested contained the yellow coloring-matter found in rabbit's urine. A portion of the standard solution and of the urine containing the unknown amount of the drug were placed in the two tubes

of a Duboscq colorimeter and the comparison made. Having thus determined the amount of phenolsulphonephthalein excreted in one hour, the percentage of the amount given was easily calculated.

From observations on a good many rabbits it was found that the phenolsulphonephthalein appeared in the urine in about twenty minutes from the time it was given subcutaneously. The time variations from this in either direction were small. Since it was not possible to catheterize the female rabbits the drug was given subcutaneously, and the animal killed in one hour and twenty minutes. The urine in the bladder was then collected and the estimation made as before. This gave a fairly accurate estimate of the per cent excreted.

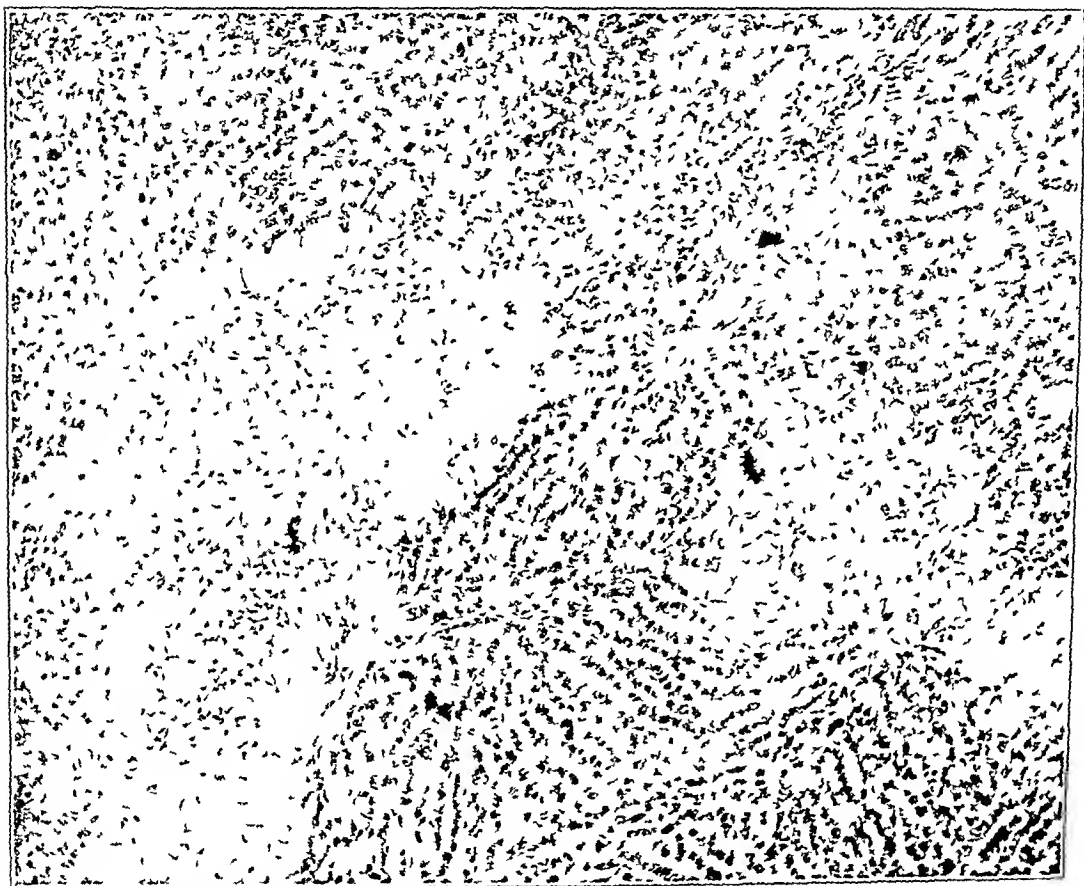


Fig 38—Rabbit 79. Liver shows irregular areas of almost complete disappearance of liver cells and their place taken by very large dilated sinusoids or lakes of blood. Magnification 125 diameters.

In the great majority of cases tested over 40 per cent of the drug was excreted in one hour, which conforms to the statement quoted at the beginning of the discussion. In a few normal rabbits tried the excretion was found to be about this per cent. Only considerably less than this was considered a delayed excretion.

Number of animals given the test 31  
 Delayed excretion 16=51.6 per cent  
 Very markedly delayed excretion 4

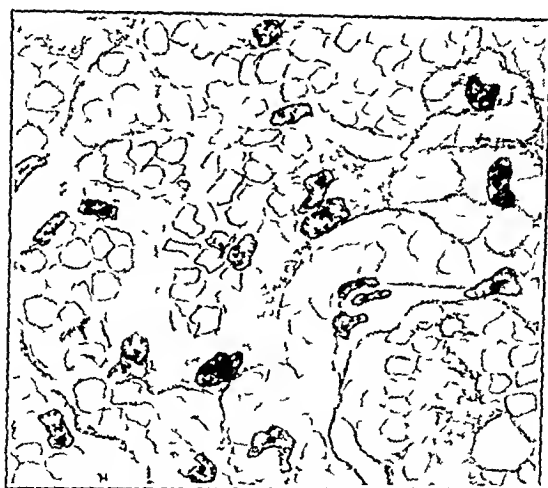


Fig 39—Rabbit 79 Shows hemorrhage about liver cells



Fig 40—Rabbit 79 Shows hemorrhage about liver cells

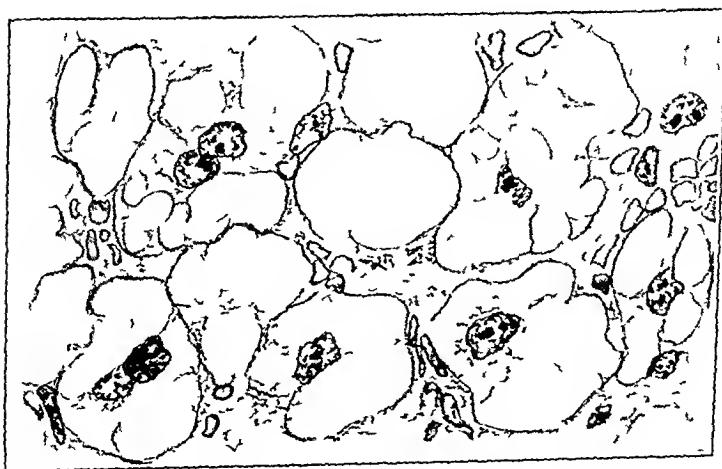


Fig 41—Rabbit 79 Shows vacuolar degeneration of liver cells

The lesions in these animals were produced as shown in Table 8

TABLE 8 —PRODUCTION OF LESIONS

	Test Tried	Delayed Excretion	Markedly Delayed Excretion
Uranum nitrate 0 002 gm every 3d day	7	5	2
Uranum nitrate 0 005 gm every 3 wks	10	4	0
Potassium bichromate 0 0125 gm every 3 weeks	9	4	1
Fowler's solution m 8-10 every 3 weeks	5	3	1
Total	31	16	4

Here, as in the other experiments, it was impossible to see any definite relation between the delayed excretion of the drug and the histological lesions in the kidney That is, the animals of the same groups as these showing delayed excretion, but in whom excretion was normal, had lesions as marked or even more so than those in which it was delayed It is interesting that some of the animals that had Fowler's solution showed delayed excretion with little visible change in kidney

It might be interesting again to compare from this new point of view the edema test and the organ weights in these animals

Of the sixteen rabbits with delayed excretion

1 Edema test tried on	16
Edema present at autopsy	4
2 Organs weighed in	16
Variation from normal	7
Small kidney, normal heart	3
Small kidney, large heart	1
Normal kidney, large heart	2
Large kidney, large heart	1

Of the four with very markedly delayed excretion

1 Edema test tried	4
Edema present	2
2 Organs weighed in	4
Variation from normal	3
Small kidney, large heart	1
Normal kidney, large heart	1
Large kidney, normal heart	1

The small number of animals experimented on makes dogmatic conclusions impossible, but it is certain from the work thus far presented that the functional capacity of the kidney evidenced in secretion of water and certain drugs cannot be estimated by histological examinations, that kidneys with the most marked histological lesions frequently have normal function, and others with apparently identical or even lesser lesions showed marked disturbance.

STUDY IX THE EFFECT OF SPARTEIN AND ADRENALIN (EPINEPHRIN) INJECTIONS ON THE KIDNEY OF THE RABBIT<sup>4</sup>

R. M. SMITH, M.D., BOSTON

Walker and Christian have described the production of cardiac lesions—myocarditis, pericarditis, endocarditis—in rabbits by the injection of spartein sulphate (0.01 to 0.04 gm.) and adrenalin (epinephrin) chlorid (0.1 to 0.2 cc of a 1-1,000 solution). In some animals the spartein was given subcutaneously and the adrenalin intravenously, but in most, both drugs were injected intravenously. I have examined the kidneys from twenty-nine of these animals.

Macroscopically the kidneys did not show any departure from the normal except in occasional instances when they appeared injected. This injection did not bear any apparent relation to the cardiac condition, but was evidently independent of it. Microscopically no lesions were found which in any way could be associated with the injection of the drugs. A few of the animals showed some spontaneous lesions as I have mentioned in connection with studies on the kidneys of rabbits which received uranium nitrate and other kidney irritants. These spontaneous lesions occurred in rabbits autopsied from one hour to two or three days after the injection of spartein—much too soon for any causal relation to exist between the drug and the histological finding in the kidney. The chronic lesions consisted of a slight connective tissue increase—in one or two instances with some dilatation of the renal tubules.

Nearly all the sections showed a marked injection of the vessels, especially those of the glomeruli and medulla. Sometimes only the vessels going in from the cortex were markedly congested. In some of the kidney this condition was extreme, making the whole section appear very red under the microscope. In no case, however, was it possible to find any evidence of the breaking through of the blood into the spaces without the vessels. Apparently simply an unusual amount of blood was present in the vessels at the time of death. An attempt was made to match up the more bloody sections with the more severe cardiac conditions, but no constant relationship was found. In some instances, however, the kidney sections of animals dying in convulsions were greatly injected, but even this was not an unfailing condition.

No tests of kidney functions were made with these animals.

So far as this study goes it supports the statement made by Fleisher and Loeb<sup>7</sup> that injections of spartein and adrenalin cause no lesions in the kidney.

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<sup>4</sup>This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

<sup>5</sup>Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D. C.

<sup>7</sup>Fleisher and Loeb. Further Investigations in Experimental Myocarditis, THE ARCHIVES INT. MED., 1910, VI, 427.

STUDY X EXPERIMENTAL MYOCARDITIS PRODUCED BY SPARTEIN SULPHATE  
AND ADRENALIN CHLORID \*

I CHANDLER WALKER, M D, BOSTON

Many observers have produced lesions of the myocardium in various ways, by the intravenous injections of cultures of *Staphylococcus pyogenes aureus* (Ribbert<sup>8</sup>), diphtheria bacilli (Babes<sup>9</sup>), diphtheria toxin (Charrin,<sup>10</sup> Welch and Flexner,<sup>11</sup> Mollard and Regaud,<sup>12</sup> and Flexner<sup>13</sup>), cultures of streptococci (Tallquist<sup>14</sup>), by ligation of coronary vessels (Baumgarten<sup>15</sup>), by exposing animals to high temperature (Zwaschkewitsch,<sup>16</sup> Litten,<sup>17</sup> Naunyn,<sup>18</sup> Nasaroff,<sup>19</sup> Werhovsky,<sup>20</sup> Welch<sup>21</sup>), by injections of adrenalin chlorid (K Ziegler,<sup>22</sup> Pearce,<sup>23</sup> Grober,<sup>24</sup> Miesowicz<sup>25</sup>), and by injections of spartein and adrenalin (Fleisher and Loeb<sup>26</sup>). The more acute lesions of the myocardium have been the ones chiefly studied by these experimenters. For the production of chronic lesions the method used by Fleisher and Loeb seems to be the most satisfactory, and has been used in the experiments here reported, which were carried on in the laboratory of the Theory and Practice of Physic in the Medical School of Harvard University at the suggestion and under the supervision of Dr H A Christian.

Rabbits were the only animals used in these experiments, and for convenience they may be grouped into five series in which the spartein

\*This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases

\*Reported at the Annual Meeting of the Association of American Physicians, May 3 5, 1910, Washington, D C

8 Ribbert Fortsch d Med, 1886, iv, 1

9 Babes Virchows Arch f path Anat, 1896, cxix, 460

10 Charrin Semaine Méd, 1890, x, 285

11 Welch and Flexner Bull Johns Hopkins Hosp, 1891, ii, 107, Bull Johns Hopkins Hosp, 1892, iii, 17

12 Mollard and Regaud Ann de l'Inst Past, 1897, xi, 97

13 Flexner Johns Hopkins Hosp Rep, 1897, vi, 259

14 Tallquist Beitr z path Anat u z allg Path (Ziegler's), 1899, xxv, 159.

15 Baumgarten Am Jour Physiol, 1899, ii, 243

16 Zwaschkewitsch Dissertation, St Petersburg, 1870

17 Litten Virchows Arch f path Anat, 1887, lxx, 10

18 Naunyn Arch f exper Path, 1884, xviii, 49

19 Nasaroff Virchows Arch f path Anat, 1882, xc, 482

20 Werhovsky Beitr z path Anat u z allg Path (Ziegler's), 1895, xviii, 72

21 Welch Med News, London, 1888, li, 365

22 K Ziegler Beitr z path Anat u z allg Path (Ziegler's), 1905, xxxviii, 229

23 Pearce Jour Exper Med, 1906, viii, 400

24 Grober Deutsch med Wehnschr, 1907, xxxiii, 744

25 Miesowicz Wien klin Wehnschr, 1909, xxi, 79

26 Fleisher and Loeb THE ARCHIVES INT MED, 1909, iii, 78 Jour Am Med Assn, 1909, lii, 1561, THE ARCHIVES INT MED, 1910, vi, 427 Strickler and Fleisher Jour Pharm and Exper Therap, 1910, ii, 55

sulphate and adrenalin chlorid were used by different methods in order to determine the most satisfactory procedure for producing experimental myocarditis

In the first series, four rabbits were injected intravenously with maximum doses of spartein sulphate,<sup>27</sup> and these injections were not followed by injections of adrenalin chlorid. The animals were injected from once to thirty times at three-day intervals

In the second series twenty-four young rabbits were injected subcutaneously with spartein sulphate 0.025 gm, followed subcutaneously in three to five minutes by adrenalin chlorid<sup>28</sup> 0.2 c c of a 1 to 1,000 solution. These injections were repeated every three days, and a pair of rabbits of approximately the same weight were killed at successive three-day intervals. In addition in this series two other rabbits received injections in the same way as the above every day for a period of six weeks, and then every other day for six weeks

In the third series were eight rabbits in which spartein sulphate was injected subcutaneously in doses of 0.025 gm, followed intravenously in five to fifteen minutes by adrenalin chlorid 0.2 c c of a 1 to 1,000 solution

In the fourth series six rabbits were injected with spartein sulphate and adrenalin chlorid, both intravenously, in small doses, repeated at three-day intervals, and extending over a long period, one to three months

The fifth series comprised eleven rabbits injected intravenously with maximum doses of spartein sulphate followed intravenously in five to fifteen minutes by adrenalin chlorid 0.2 c c of 1 to 1,000 solution

The rabbits in all series either died or were killed at varying time intervals after the first injection, and so received a varying number of injections of varying size given in varying combinations

No animals died from the effect of spartein sulphate when injected subcutaneously, but there were several deaths due to the drug when given intravenously. The animals died with either respiratory paralysis, gasping for breath, or with convulsions, or with both. Death may be avoided by slowly injecting the drug with frequent pauses, thereby allowing a mixture of the drug with the blood in the circulation and much greater doses may be safely used in this way. Some rabbits seem to be more susceptible to spartein than others, since several rabbits of the same weight and age may survive the same injection, while one or two others will not. Only two deaths out of about thirty rabbits used could be considered due to adrenalin chlorid used intravenously, and these had received spartein just previously. The deaths were convulsive with respiratory paralysis. The best lesions were produced by maximum doses of spartein given intravenously (making the animal as weak and stupid as

<sup>27</sup> Merck's preparation of spartein sulphate was used throughout

<sup>28</sup> Parke, Davis & Co's preparation of adrenalin chlorid was used throughout



possible and still survive) followed intravenously in a few minutes by adrenalin. Adrenalin given subcutaneously had no effect.

All animals injected intravenously with one or two large doses of spartein followed intravenously by adrenalin at autopsy showed much blood-stained fluid in the pericardial, thoracic and abdominal cavities. A smaller amount of less bloody fluid was found in these cavities when the spartein was used subcutaneously followed by adrenalin intravenously. After two injections the fluid seemed to be absorbed and no further exudation appeared to take place, as none was present in rabbits dying after three or more injections.

The methods used in this experimental work having been briefly described, the various series will now be taken up and the lesions described.

**SERIES 1**—Four rabbits injected with spartein sulphate 0.025 gm intravenously without adrenalin. One rabbit was killed a few minutes after injection, and showed slight congestion. Another was killed four hours after injection and showed marked congestion, and a distinct focus of deeper congestion on surface of left ventricle. A third rabbit was injected every three days for twenty-five injections and another rabbit for thirty injections. Both of these showed simply a congestion of the myocardium. In these two rabbits the spartein was gradually increased until they received 0.05 gm several times. Thus it is seen that spartein alone, given in twice the amount which with adrenalin will cause a lesion, produces no lesions.

**SERIES 2**—Twenty-four rabbits were selected, weighing between 1100 and 1400 gm, paired according to weights and were injected subcutaneously at three-day intervals with spartein sulphate 0.025 gm, followed subcutaneously in three to five minutes with adrenalin chlorid 0.2 cc of a 1 to 1,000 solution. Two rabbits were killed three days following the first injection, two more three days after a second injection, and this was repeated until the last two rabbits of this series were killed. Of these twenty-four rabbits, two were discarded after three injections because one of the rabbits contracted an infection. No macroscopic lesions could be observed in any of the rabbits of this series.

Microscopically in three rabbits (No 167, eight injections, No 169, nine injections, No 171, ten injections) there was moderate capillary congestion distinctly in excess of that shown by other animals of the series. In four rabbits (No 152, one injection, No 156, three injections, No 165 and No 166, seven injections), there was an increased interstitial cellularity. These cells were of the connective tissue type, not uniformly scattered through the myocardium, but occurring in foci. This change was more extensive in the animals receiving the larger number of injections, being very slight in Rabbit 152. A somewhat similar picture (Fig 3) was presented by an animal (Rabbit 79) of a different series from the ones described in this paper. In two rabbits (No 159, four injections, No 163, six injections) there were small foci of young connective tissue. Rabbit 159 showed more of this than Rabbit 163. In none of these rabbits was the lesion extensive, and even where most marked it constituted only a slight departure from the normal.

Two more rabbits were injected subcutaneously with the same dosage as in the preceding series every day for six weeks and then every other day for six additional weeks. One showed no lesion. The other had a large area of old fibrous tissue practically replacing the muscle, with only little shreds of muscle left. These muscle fibers were devoid of nuclei and often took the eosin stain deeply, the cross striations being lost. This fibrous tissue was very near the

septum at the base of the left ventricle, and it is a question whether it was due to the drugs or whether it was a spontaneous lesion. In its distribution and character it did not resemble a spartein and adrenalin lesion. These protocols will not be given.

It was noted that injecting both spartein and adrenalin at the same site on the same day caused a necrosis and sloughing of the tissues, whereas separated injections on the same day produced no necrosis.

**SERIES 3**—Eight rabbits were injected subcutaneously with spartein sulphate 0.025 gm followed in about ten minutes intravenously by adrenalin chlorid 0.2 cc, 1:1000 solution. Only four protocols will be given, the others being duplicates.

Rabbit 274 was injected subcutaneously with spartein 0.025 gm followed intravenously in ten minutes by adrenalin solution<sup>29</sup> 0.2 cc. This animal died twenty minutes later with respiratory paralysis and convulsions. Microscopically only congestion was present. Rabbit 268, similarly injected at three day intervals, showed a capillary congestion (Fig 7) as in Rabbit No 274.

Rabbit 279, weight 1450 gm, was injected subcutaneously with spartein 0.025 gm, followed intravenously in ten minutes by adrenalin solution 0.2 cc. Five days later the same was repeated and the rabbit died about ten minutes following this injection. At autopsy there was an increased amount of a straw colored fluid in all body cavities. Microscopically there was a patchy cellular infiltration throughout the myocardium. In some of these foci many lymphoid cells were present. This was particularly the case in the subpericardial layers. There was also an increased amount of connective tissue about the blood-vessels. Where the round cells showed only a slight increase, the muscle fibers were hypertrophied, showed very marked branching, and an increased number of nuclei, as many as five or six in a line. Where there was considerably increased cellularity (Fig 4), the muscle was much degenerated, with loss of striations, and in places where the young cells appeared as stellate figures with beginning fibrils, the muscle was atrophied and replaced by new tissue.

Rabbit 277, weight 1480 gm, was injected subcutaneously with spartein 0.025 gm followed intravenously in ten minutes by adrenalin solution 0.2 cc, this being repeated every three days for a period of twelve days, thus four injections were given. The rabbit died a few minutes after the last injection. At autopsy considerable free bloody fluid was present in all the cavities, and in addition considerable fibrin in the pericardial cavity, with a slight roughening of the surface of the left ventricle. The heart was large. Microscopically the same general picture was seen as in Rabbit 279, but the process was somewhat more advanced and more extensive. The connective tissue was older, with more fibrils and less cells present, the arterial walls were more thickened, the muscle more extensively atrophied.

Rabbit 284, weight 2200 gm, was injected with spartein sulphate 0.025 gm followed intravenously in ten minutes by adrenalin solution 0.2 cc at four day intervals over a period of two months, sixteen injections in all. At autopsy no fluid was present, the heart was large and firm. Microscopically a slight increased cellularity diffusely situated was seen, the arterial walls were thickened, and the muscle was hypertrophied.

**SERIES 4**—Here six rabbits were used, but as they all showed a similar condition only one protocol will be given. These animals were injected intravenously with small doses of spartein and adrenalin.

Rabbit 282, weight 1920 gm, was injected with spartein sulphate 0.007 gm followed in about ten minutes by adrenalin solution 0.1 cc, both intravenously. This was repeated at three-day intervals for seven times, then the spartein was increased to 0.008 gm and the injections repeated at three day intervals for seven more times, in all fourteen injections extending over two months' time. At

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<sup>29</sup> Adrenalin solution whenever used means a 1 to 1,000 solution of adrenalin chlorid.

bloody fluid filled the pericardial cavity. The heart was very large, and left autopsy there was fluid in the abdominal and thoracic cavities, and a muddy auricle and ventricle very firm and thickened, with a white fibrous patch at the base of the left ventricle. Microscopically there was a diffuse increased cellularity of the myocardium with an hypertrophy of muscle fibers, with increased numbers of nuclei, nuclei swollen and nucleoli prominent. The connective tissue about the blood-vessels was thickened. In addition there was a large fibrous patch at the base of the left ventricle entirely replacing the muscle. The other five animals did not show such a fibrous area as described in Rabbit 282, but were duplicates in every other way. The striking change in this series was slight diffuse increased interstitial cellularity, interstitial edema, and moderate connective tissue increase and hypertrophy of muscle (Fig 2).

SERIES 5—In this series eleven rabbits were injected intravenously with spartein sulphate and adrenalin chlorid in the following way. Spartein sulphate was injected intravenously in maximum doses, that is as large a dose as the rabbit appeared able to stand. Shortly after such a dose the rabbit would seem very tired with rapid respiration and a rapid, unsteady heart. After an interval of ten to twenty minutes adrenalin solution was injected intravenously with a dose of 0.2 c.c. The adrenalin appeared to produce no marked effect except possibly to accentuate somewhat the already existing symptoms.

One of these rabbits was killed three minutes after the adrenalin chlorid injection, and nothing abnormal was seen.

Another (Rabbit 290) was killed four hours after injection, and at autopsy an area of marked congestion about half a centimeter in diameter, of a bloody red color was situated in the center of the wall of the left ventricle. Microscopically in the animal there was congestion of the subpericardial myocardium as follows. Rabbit 290, weight 1480 gm., injected intravenously with spartein sulphate 0.04 gm., followed in ten minutes intravenously by adrenalin solution 0.2 c.c. The rabbit became very tired and listless, respiration rapid, heart rapid and fluttering, three hours later heart seemed steadier, but animal was very stupid. Four hours after injection the rabbit was killed. Macroscopically there was a bloody red area of congestion on the wall of the left ventricle near the center about 0.5 cm. in diameter. Microscopically there was congestion and edema of the subpericardial myocardium of the left ventricle.

The third rabbit, No. 296, weight 1750 gm., was injected intravenously with spartein sulphate 0.035 gm. followed in ten minutes by adrenalin solution 0.2 c.c. The rabbit seemed very tired after this. It was killed twenty-four hours after injection. At autopsy the thoracic cavity contained much very bloody fluid and the pericardial cavity was filled with bloody fluid. The heart showed areas of congestion of a bright red color on the surface of the right auricle, to a slight extent on the left auricle, and on the surface of the left ventricle an area of dark brownish-red color with slight peripheral congestion. Microscopically in the myocardium of the right and left ventricles there was a very general indistinctness of muscle striations, a diffuse increased interstitial cellularity, and quite a general capillary congestion. In places muscle fibers were markedly degenerated, appearing as deeply staining fibers with very indistinct striation. Some muscle fibers had lost practically all striation. Besides the diffuse cellularity there were very cellular foci in association with markedly degenerated muscle fibers. In places cells have invaded muscle fibers, and hyaline fragments of muscle fibers may be seen scattered among these cells. The cells themselves were not definitely phagocytic, however, for muscle fragments. These cells were of the young connective tissue and endothelial types. Their nuclei were vesicular with fairly fine chromatin granules, and one to three coarser chromatin masses. In some there was a round reddish staining nucleolar mass. The cytoplasm of these cells was very finely granular and usually distinctly basophilic. There was no evident cell membrane. Polynuclear leukocytes play but a small part in the process, a few were found scattered between the muscle fibers, more numerous about the cell foci described above.

A fourth rabbit, No 293, received intravenously 0.04 gm spartein sulphate and ten minutes later intravenously 0.2 cc adrenalin solution. This animal seemed very tired and quiet after the injection similarly to No 296, and was killed at the end of thirty-two hours. At autopsy there was a slight amount of a straw colored fluid in the abdominal cavity, very much and rather bloody fluid in the thorax, while the pericardial cavity was filled with a very bloody fluid, and the pericardial sac seemed to be slightly glued in places to the left ventricle. Areas of fresh hemorrhage were present on the right auricle, much more marked and wide spread on the left ventricle. Microscopically a very similar picture was seen to that in Rabbit 296. There was evidence of a diffuse degeneration of muscle fibers as in the former. The interstitial cells were more definitely of the connective tissue type with processes and more connective tissue fibrils have been formed. Near the apex of the left ventricle there was a cellular focus of considerable size about much degenerated muscle fibers. Mitotic figures were frequent in this area. In the right ventricle near the auriculoventricular groove there was another focus of cells of young connective tissue type with many polynuclear leukocytes and few plasma cells.

The fifth rabbit, No 280, weight 1580 gm, was injected with spartein sulphate 0.03 gm, followed in about five minutes by adrenalin solution 0.2 cc, both drugs given intravenously. After five days the rabbit was killed. At autopsy much free blood stained fluid was found in the abdominal cavity, with little flakes of fibrin floating on the intestines, still more bloody fluid in the thoracic cavity, and the pericardial cavity was filled with very bloody fluid. A small roughened area was present on the surface of the left ventricle. Microscopically the subpericardial myocardium was very extensively infiltrated with connective tissue, which was moderately cellular. Where there was a larger amount of connective tissue the muscle fibers were much atrophied and evidently numerous fibers had entirely disappeared. From this point the young connective tissue extended deeper into the myocardium interlacing with the muscle bundles. The muscle fibers frequently showed a large perinuclear non striated area and two or three nuclei were often seen in a fiber. An area of practically normal muscle was present in the center of the wall of the left ventricle, although there was an increased interstitial cellularity. As the endocardium was approached, the connective tissue increased in certain foci and degeneration of the muscle was more extensive.

The sixth rabbit of this series, No 270, weight 2370 gm, was injected intravenously with spartein sulphate 0.025 gm, followed in fifteen minutes intravenously with adrenalin solution 0.2 cc. This was repeated three days later and the animal died four days after the second injection, that is seven days after the first injection. At autopsy the abdominal cavity contained 60 cc of free blood-stained fluid, the thoracic cavity 18 cc and the pericardial cavity was filled with very bloody fluid. The heart muscle was pale. Microscopically there was an increased interstitial cellularity with moderate connective tissue increase.

The seventh rabbit, No 292, weight 1750 gm, was injected intravenously with 0.03 gm spartein followed intravenously in fifteen minutes by adrenalin solution 0.2 cc, this was repeated two days later and the animal was killed twenty-four hours after the second injection, that is, three days after the first injection. Here larger doses of spartein were given with a shorter interval between. Macroscopically there was an area near the apex on the left ventricle of a brownish color, where the muscle was soft, pale and flabby. Microscopically there was a very great increase of young cellular connective tissue in many places very largely replacing muscle fibers. In other places atrophied and degenerated fibers were scattered in the young connective tissue. Mitoses of connective tissue cells were numerous. This increased cellularity was situated in both walls of the left ventricle throughout the central portion, the base and the apex of the heart being entirely free from pathological change. The whole muscle in the degenerated area was riddled with young connective tissue. Slight congestion was also present.

The remaining rabbits of this series were duplicates of the above, and will not be described. Rabbits receiving such large amounts of spartein would not survive a third injection.

### *Summary*

A total of fifty-seven rabbits were used in these experiments with the following results. A series of four rabbits received intravenously spartein sulphate alone in large doses and showed only congestion of the myocardium. In the second series of twenty-four rabbits receiving spartein sulphate followed by adrenalin chlorid, both subcutaneously, three rabbits showed capillary congestion of the myocardium (Fig 1) and six showed very slight increased cellularity of the young connective tissue type. Where the change was most marked in this series it constituted only a slight departure from the normal. In addition two other rabbits of this series were injected with the same dosage and in the same manner only daily for six weeks and thereafter every second day for six weeks more, one was negative, and the other had an extensive fibrous area in the myocardium at the base of the left ventricle near the septum. It is uncertain whether the latter lesion was due to the drugs or whether spontaneous, however, it seems more likely to have been spontaneous.

The eight rabbits of the third series were injected subcutaneously with spartein sulphate, 0.025 gm., followed intravenously in about ten minutes by adrenalin solution, 0.2 cc. At a twenty-five minute interval after injection, congestion of the myocardium was noted, at a five-day interval fluid was found in all the body cavities and microscopically a patchy cellular infiltration of the myocardium as follows: in the subpericardial myocardium were small foci of lymphoid and young connective tissue cells, there was an increased amount of connective tissue about the blood-vessels, and in the myocardium, where there was only slight cellular increase, the muscle showed evidences of hypertrophy, where there was considerable cellular increase, the muscle showed evidences of degeneration. In another rabbit, which received in the same manner four injections extending over a period of twelve days, autopsy showed bloody fluid in all the body cavities, a roughening of the left ventricle and a large heart. Microscopically was noted a similar picture to that seen in the previous rabbit, only more extensive and more advanced. The last rabbit of this series was injected like the above rabbits for sixteen times, extending over a period of two months, and this rabbit showed a diffuse increased cellularity, thickened arterial walls and muscle hypertrophy. In the fourth series of six rabbits injected with spartein sulphate in small doses followed in ten to twenty minutes by adrenalin solution, 0.2 cc., both drugs given intravenously, all showed a similar lesion. At autopsy there was fluid in all body cavities and blood in the pericardial cavity, several showed also macroscopically a lesion of the left heart. Micro-

scopically there was a diffuse increased cellularity of the myocardium with an hypertrophy of the muscle and thickened walls of the blood-vessels. In addition one rabbit showed a large fibrous patch at the base of the left ventricle entirely replacing the muscle. In the last series eleven rabbits were injected intravenously with maximum doses of spartein sulphate followed intravenously in ten to twenty minutes by adrenalin solution, 0.2 c.c., and the rabbits were killed at varying intervals. At a four-hour interval there was both macroscopic and microscopic congestion of the left ventricle, at twenty-four and thirty-two-hour intervals there was bloody fluid in the body cavities, areas of congestion over the surfaces of the heart and microscopically a diffuse increased cellularity with capillary congestion and muscle degeneration. At five-day intervals the same picture was seen only more advanced and more extensive with greater muscle degeneration. Grossly there was a roughened area on the surface of the left ventricle. Those rabbits surviving two injections showed very great increased cellularity and marked muscle degeneration.

The histology of the myocardial lesions so produced can be described somewhat more consecutively as follows. Very shortly after a dose of spartein sulphate is given, especially when this is followed by an intravenous injection of adrenalin chlorid, a capillary congestion appears (Fig 1), whether the drugs have been given several times previously or not. The congestion is probably transitory, for a later stage is represented by interstitial edema (Fig 2), with which may be associated some connective tissue proliferation (Figs 2 and 3). Another effect of these drugs is the production of cellular foci made up of lymphoid, plasma and young connective tissue cells (Fig 4), usually about necrosed or severely injured muscle cells (Fig 4). At other times the connective tissue proliferation is rather more diffuse, replacing muscle cells and extending among and separating degenerated muscle cells (Figs 5 and 6). The exact histological picture varies with the age of the lesion. In some hearts a quite actively proliferating cellular stroma is seen (Figs 5 and 6), in others there is adult connective tissue but slightly infiltrated with cells (Fig 7).

From these results it appears that subcutaneous doses of spartein, followed intravenously by adrenalin, as well as small doses of spartein, followed by adrenalin, both intravenously, produce a moderate cellularity with slight muscle hypertrophy, while maximum doses of spartein, followed by adrenalin, both given intravenously, produce very marked cellularity, which goes on to fibrous tissue formation associated with extensive degeneration of the muscle. This latter method seems the most satisfactory procedure for producing chronic myocarditis. By comparing

these lesions with the descriptions of hypertrophy found in the human heart as described by Albrecht,<sup>30</sup> Krehl<sup>31</sup> and others,<sup>32</sup> there seems to be a striking familiarity

Carney Hospital

# STUDY XI EXPERIMENTAL PERICARDITIS PRODUCED BY SPARTEIN SULPHATE AND ADRENALIN CHLORID

I CHANDLER WALKER, M D, AND HENRY A CHRISTIAN, M D, BOSTON

This paper is a study of the pericardia of the hearts of rabbits used in the production of experimental myocarditis by the injection of spartein sulphate and adrenalin chlorid. The work was carried on in the laboratory of the Theory and Practice of Physic in the Medical School of Harvard University.

There seems to have been very little previous work done on experimental pericarditis. Fleisher and Loeb<sup>33</sup> in their paper on Experimental Myocarditis mention an accompanying pericarditis, but they do not describe it. In a second paper<sup>34</sup> they state that six rabbits in a series of forty-two animals showed a pericarditis in five associated with pneumonia. They state that "it appears improbable that the injection of spartein and adrenalin produced the pericarditic lesion in the same direct way as it did the myocarditis." No other references to lesions of this type were found.

Rabbits were the only animals used in the experiments here described. For convenience these animals are grouped into five series in which the spartein sulphate and adrenalin chlorid were used by different methods in order to determine the most satisfactory procedure for producing experimental cardiac lesions. For a description of each series with details of methods used and results obtained, the reader is referred to the previous paper, "Experimental Myocarditis Produced by Spartein Sulphate and Adrenalin Chlorid." In this place only the pericardial changes will be described.

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30 Albrecht. *Der Herzmuskel*, Berlin, 1903.

31 Kiehl. *Deutsch Arch f klin Med*, 1890, xlv, 454, 1891, xlviii, 414, Nothnagel's *Specielle Pathologie und Therapie*, xv.

32 Stadler. *Deutsch Arch f klin Med*, 1907, xc, 98.

33 Fleisher and Loeb. *Experimental Myocarditis*, *THE ARCH INT MED*, 1909, iii, 78.

34 Fleisher and Loeb. *Further Investigations in Experimental Myocarditis*, *THE ARCHIVES INT MED*, 1910, vi, 427.

SERIES 1—Four rabbits injected intravenously with spartein sulphate<sup>35</sup> 0.025 gm without adrenalin chlorid. One rabbit killed a few minutes after injection and showed no lesion of the pericardium. Another was killed four hours after injection and showed an area of congestion in the surface of the left ventricle, and microscopically an occasional red blood-cell in the fibrous tissue of the pericardium. A third was injected every three days for twenty-five injections and another rabbit for thirty injections. Both of these showed in their pericardia a few scattered red blood-cells and an occasional area where there were many red cells. In these two rabbits the spartein was gradually increased until they received 0.05 gm several times.

SERIES 2—Twenty-four rabbits were selected, weighing between 1100 and 1400 gm, paired according to weights and were injected subcutaneously at three-day intervals with spartein sulphate 0.025 gm, followed subcutaneously in three to five minutes with adrenalin chlorid 0.2 cc of a 1 to 1000 solution<sup>36</sup>. Two rabbits were killed three days following the first injection, two more three days following the second injection, and this was repeated until the last two rabbits of this series were killed. Of these twenty-four rabbits, two were discarded after three injections because one of the rabbits contracted an infection. No macroscopic or microscopic lesions could be observed in the pericardium of any of the rabbits of this series.

Two more rabbits were injected subcutaneously with the same dosage as in the preceding series every day for six weeks and then every other day for six additional weeks. These two rabbits showed no macroscopic or microscopic lesions of the pericardium.

SERIES 3—Eight rabbits were injected subcutaneously with spartein sulphate 0.025 gm, followed in about ten minutes intravenously by adrenalin chlorid 0.2 cc, 1 to 1000 solution.

Rabbit 274 was injected subcutaneously with spartein sulphate 0.025 gm, followed intravenously in ten minutes by adrenalin chlorid 0.2 cc, 1 to 1000 solution. This animal died twenty minutes later with respiratory paralysis and convulsions. Microscopically the pericardium was congested and edematous, red blood-cells were scattered throughout the fibrous tissue. Rabbit 273 similarly injected, died the same day and showed a slight hemorrhagic exudation into the pericardium (Fig 19).

Rabbit 279, weight 1450 gm, was injected subcutaneously with spartein sulphate 0.025 gm, followed in ten minutes by adrenalin chlorid 0.2 cc, 1 to 1000 solution. Five days later the same was repeated and the rabbit died about ten minutes following this injection. At autopsy there was an increased amount of a straw colored fluid in all the body cavities. Microscopically there was slight thickening of the pericardium with increased cellularity, and edema, especially of that part of the pericardium adjoining the myocardium (Fig 20). The cells present were of the young connective tissue and lymphoid types, with a rare polynuclear leukocyte. The pericardium of the left ventricle was the seat of this lesion.

Rabbit 268, weight 1580 gm, was injected subcutaneously with spartein sulphate 0.025 gm, followed intravenously in ten minutes by adrenalin chlorid 0.2 cc, 1 to 1,000 solution. Three days later the injection was repeated, and again in four days, when the rabbit died five minutes after the spartein injection. Thus this animal survived two injections extending over a period of seven days. At autopsy there was a small amount of clear straw colored fluid in all the body cavities. Microscopically there was slight thickening of the pericardium with slight edema and congestion, increased vascularity and cellularity (Fig 21).

Rabbit 277, weight 1480 gm, was injected subcutaneously with spartein sulphate 0.025 gm, followed intravenously in ten minutes by adrenalin chlorid

<sup>35</sup> Merck's preparation of spartein sulphate was used throughout.

<sup>36</sup> Parke, Davis & Co's preparation of adrenalin chlorid solution was used throughout.



0.2 cc, 1 to 1000 solution, this being repeated every three days for a period of twelve days, thus four injections were given. The rabbit died a few minutes after the last injection, only surviving three injections. At autopsy considerable free bloody fluid was present in all the cavities and in addition considerable fibrin in the pericardial cavity, with slight roughening of the surface of the left ventricle. The heart was large. Microscopically the same general picture was seen as in No 268, but the process was more extensive, the whole thickness of the pericardium being involved, and the pericardium was also more cellular.

Two other rabbits were injected over a long period of time. Rabbit 278, weight 1480 gm, received thirteen injections at three day intervals, and No 285, weight 2200 gm, was given thirty injections during a period of three months, both of these rabbits getting the same doses under the same conditions as the previously described animals. Microscopically there was a slight increased cellularity of the connective tissue type. The cells appeared in foci scattered along the juncture of the pericardium and myocardium.

**SERIES 4**—Here six rabbits were used and were injected intravenously with small doses of spartein and adienalin.

Rabbit 267, weight 1520 gm, was injected intravenously with spartein sulphate 0.025 gm, followed intravenously in ten to twenty minutes by adienalin chlorid 0.2 cc, 1 to 1000 solution. This was repeated seven times at three-day intervals for a period of about a month, when the rabbit died immediately following the ninth injection. Microscopically in places in the pericardium of the left ventricle there were foci of lymphoid cells and young connective tissue cells with congestion. In other places there were chiefly young connective tissue cells, and in still other places only red blood-cells were noted.

Rabbit 272, weight 2750 gm, was injected intravenously with varying doses of spartein sulphate from 0.025 gm to 0.05 gm, followed intravenously in ten to twenty minutes by adienalin chlorid 0.2 cc, 1 to 1000 solution. These injections extended over a period of three months at three day intervals, so that the rabbit received in all twenty-five injections. At autopsy the heart was large, firm, with whitish areas of thickening on the wall of the left ventricle. Microscopically a very similar picture to No 267 was seen.

Rabbit 275, weight 2450 gm, was injected in the same manner and the same number of times as No 267. At autopsy there was much fluid in the abdominal cavity. Microscopically a similar picture to that in No 267 was seen with the exception that the right ventricle showed the lesion.

Rabbit 265, weight 1200 gm, was injected intravenously with spartein sulphate in varying doses from 0.0125 gm to 0.025 gm, followed intravenously in ten to twenty minutes by adienalin chlorid 0.2 cc, 1 to 1000 solution, in all eighteen injections during two months' time at three day intervals. Microscopically at the base of the left ventricle the denser pericardial layer was separated from the underlying muscle by a tissue of increased cellularity, with young connective tissue cells, plasma cells and red blood-cells.

Rabbit 282, weight 1920 gm, was injected intravenously with spartein sulphate 0.007 gm, followed intravenously in ten minutes by adrenalin chlorid 0.1 cc, 1 to 1000 solution repeated at three day intervals for seven times, then the spartein was increased to 0.008 gm and the injections repeated at three day intervals for seven more times, in all fourteen injections extending over two months' time. At autopsy there was fluid in the abdominal and thoracic cavities, and a muddy bloody fluid filled the pericardial cavity. The heart was very large, the left auricle and ventricle were very firm and thickened, with a white fibrous patch at the base of the left ventricle. Microscopically throughout the pericardium of both the left auricle and left ventricle there was considerable increased cellularity of the lymphocyte and young connective tissue types with edema and congestion. This was most marked at the myocardial margin.

**SERIES 5**—In this series eleven rabbits were injected intravenously with spartein sulphate and adienalin chlorid in the following way. Spartein sulphate was injected intravenously in maximum doses, that is, as large a dose as the

rabbit appeared able to stand. Shortly after such a dose the rabbit would seem very tired with rapid respiration and a rapid unsteady heart. After an interval of ten to twenty minutes adrenalin chlorid was injected intravenously with a dose of 0.2 cc of a 1 to 1000 solution. The adrenalin appeared to produce no marked effect except possibly to accentuate somewhat the already existing symptoms.

One of these rabbits, No 276, was killed three minutes after the adrenalin injection, and nothing abnormal was seen.

Rabbit 290, weight 1480 gm, was injected intravenously with spartein sulphate 0.04 gm, followed intravenously in ten minutes by adrenalin chlorid 0.2 cc of a 1 to 1000 solution. This rabbit became very tired and listless, respiration rapid, heart rapid and fluttering, three hours later the heart seemed steadier, but the animal was very stupid. Four hours after injection the rabbit was killed. At autopsy the large blood-vessels were tied and the heart and pericardium were removed *in toto* without being opened in order to avoid hemorrhage within the pericardial cavity from trauma or mechanical causes, the heart and pericardium were hardened *in toto*. Macroscopically there was a bloody red area of congestion on the wall of the left ventricle near the center about 0.5 cm in diameter. Microscopically there were areas of hemorrhage and edema in the pericardium of the left ventricle, also the pericardium was torn and raised away from the myocardium in numerous places where the congestion of the subpericardial myocardium was greatest.

The third rabbit, No 296, weight 1750 gm, was injected intravenously with spartein sulphate 0.035 gm, followed intravenously in ten minutes by adrenalin chlorid 0.2 cc of a 1-to 1000 solution. The rabbit seemed very tired after this. It was killed twenty-four hours after injection. At autopsy the thoracic cavity contained much very bloody fluid and the pericardial cavity was filled with bloody fluid. The heart showed areas of congestion of a bright red color on the surface of the right auricle, to a slight extent on the left auricle, and on the surface of the left ventricle an area of dark brownish red color with slight peripheral congestion. The heart and the pericardium were removed intact after the large blood-vessels were tied, and thus were hardened. Microscopically the pericardium was somewhat thickened with slight increased cellularity, edema and congestion. The types of cells were lymphoid cells, an occasional leukocyte, young connective tissue and endothelial cells having faintly staining, hazy and indistinct nuclei placed centrally in a scanty, faintly staining protoplasm. The pericardium of both auricles and both ventricles was similarly affected, although more cellular in some areas than others. The outer pericardium or sac showed a similar picture.

A fourth rabbit, No 293, received intravenously 0.04 gm of spartein sulphate and ten minutes later intravenously 0.2 cc adrenalin chlorid, 1 to 1000 solution. This animal seemed very tired and quiet after the injection similarly to No 296, and was killed at the end of thirty-two hours. At autopsy there was a slight amount of a straw-colored fluid in the abdominal cavity, very much and rather bloody fluid in the thoracic cavity, while the pericardial cavity was filled with a very bloody fluid, and the parietal pericardium seemed to be glued in places to the left ventricle. Areas of fresh hemorrhage were present on the right auricle, much more marked and wide spread on the left ventricle. The heart and pericardium were removed and hardened intact as previously. Microscopically a very similar picture was found to that seen in No 296, only slightly more advanced, more extensive and more cellular. In addition there were many more leukocytes and much fibrin. These sections were stained for bacteria but none could be made out. The pericardium of the left ventricle was most affected. The parietal pericardium showed a similar picture.

The fifth rabbit, No 280, weight 1580 gm, was injected with spartein sulphate 0.03 gm, followed in about ten minutes by adrenalin chlorid 0.2 cc, 1 to 1000 solution, both drugs given intravenously. After five days the rabbit was killed. At autopsy much free blood-stained fluid was found in the abdominal

cavity, with little flakes of fibrin floating on the intestines, still more bloody fluid in the thoracic cavity, and the pericardial cavity was filled with very bloody fluid. A small roughened area was present on the surface of the left ventricle. Microscopically the pericardium was slightly thickened. The normal fibrous tissue of the pericardium showed slight congestion, edema and a few young connective tissue cells. The area where the pericardium joins the myocardium was thickened with a greatly increased number of connective tissue cells, scattered lymphoid cells, increased vascularity with congestion, edema, and an occasional leukocyte. The left ventricle was affected.

The sixth rabbit of this series, No 270, weight 2370 gm, was injected intravenously with spartein sulphate 0.025 gm, followed intravenously in fifteen minutes with adrenalin 0.2 cc. The same was repeated three days later and the rabbit died four days after the second injection, that is seven days after the first injection. At autopsy the abdominal cavity contained 60 cc of free blood stained fluid, the thoracic cavity 18 cc, and the pericardial cavity was filled with very bloody fluid. The heart muscle was pale. The heart and pericardium were removed *in toto*. Microscopically (Fig 22) a similar picture was seen to that in No 280, and in addition an acute process, so that the pericardium was considerably thickened.

The seventh rabbit, No 292, weight 1750 gm, was injected intravenously with 0.03 gm spartein sulphate followed intravenously in fifteen minutes by adrenalin chlorid 0.2 cc, 1-to-1000 solution, this was repeated two days later and the animal was killed twenty-four hours after the second injection, that is, three days after the first injection. Macroscopically there was an area near the apex on the left ventricle of a brownish color, where the muscle was soft, pale and flabby. Microscopically a very similar picture to No 296 and No 270 was found, only with more thickening and more cells, more extensively distributed.

The description of a rabbit of another series of experiments is inserted here as it furnishes an intermediate stage in the pericardial lesion undoubtedly produced in the same way as in the preceding animal, though not the same procedure was followed. This is Rabbit 79, treated as follows. Spartein sulphate 0.021 gm was given subcutaneously followed by adrenalin chlorid, 1 to 1,000 solution, 0.2 cc, subcutaneously. These injections were repeated four times in the next four months in the same way, except that the last dose of adrenalin chlorid was given intravenously. At autopsy two weeks after the last injection, the pericardium appeared more opaque and thicker than normal. Microscopically in place of the rather thin, cell-poor pericardium there was a thick layer of vascular cellular connective tissue (Fig 23) in every way similar to young granulation tissue.

Rabbit 266, weight 1240 gm, was injected intravenously with spartein sulphate 0.025 gm, followed intravenously in ten to twenty minutes by adrenalin chlorid 0.2 cc. This was repeated at three day intervals for five times. After injection the rabbit became so tired with rapid respiration that three days later the dose of spartein was reduced to 0.018 gm followed in ten to twenty minutes by adrenalin 0.2 cc, both intravenously. Again the rabbit was much exhausted and three days later the dose of spartein was reduced to 0.0125 gm, followed in ten to twenty minutes by adrenalin 0.2 cc, both intravenously. The rabbit was much exhausted, tired and listless, with rapid respiration, but forceful and steady heart. The rabbit died three quarters of an hour later. At autopsy there was a slightly increased amount of muddy fluid in the pericardial cavity. Dense fibrous adhesions extended from the parietal pericardium to the auricle and ventricle of the left heart. Microscopically there was a much thickened cellular vascular pericardium with papilla formation on the surface of the left ventricle (Fig 24), a typical granulation tissue.

The remaining rabbits of this series were duplicates of the above and will not be described.

*Summary*

Although the number of rabbits used in some of these experiments is rather small, fairly definite conclusions are evident

Sparteine sulphate in large doses, injected intravenously alone, will produce no lesion of the pericardium, except congestion. Five rabbits were used.

Sparteine sulphate injected subcutaneously, followed by adrenalin chlorid subcutaneously, produces no lesion of the pericardium. In this series twenty-four rabbits were used.

Sparteine sulphate injected subcutaneously, followed in ten minutes intravenously by adrenalin chlorid, 0.2 c c of a 1-to-1,000 solution, does produce a pericarditis. First, congestion and edema are produced, these being noted as early as twenty-five minutes after the adrenalin injection. Later there is hemorrhage into the pericardial cavity. At a five-day interval there is an increased cellularity, the cells being of the young connective tissue and lymphoid types. The same drugs repeated more frequently in the same dosage and the same manner produce a more advanced and more extensive lesion with increased vascularity. At autopsy in those animals surviving for a few days, fluid is found in the body cavities. In all rabbits the lesion is in the pericardium of the left ventricle. Eight rabbits were used in this series.

In the series of six rabbits injected intravenously with small doses of sparteine sulphate, followed in ten to twenty minutes intravenously by adrenalin chlorid, 0.2 c c of a 1-to-1,000 solution, an increased cellularity is produced. The lesion is usually confined to the pericardium of the left ventricle (with the exception of one rabbit, in which both the right and left ventricles were affected, and one rabbit in which only the pericardium of the right ventricle was affected).

The series of eleven rabbits injected intravenously with sparteine sulphate in maximum doses, followed intravenously by adrenalin chlorid, 0.2 c c, show a progressive lesion of the pericardium depending upon the length of time the animal survived and the number of doses given. At a four-hour interval a macroscopic area of congestion over the surface of the left ventricle, and microscopically hemorrhage and edema of the pericardium of the left ventricle were seen. At twenty-four and thirty-two hour intervals macroscopically were noted bloody fluid in the pericardial cavity, and areas of old congestion, and microscopically increased cellularity of the young connective tissue and lymphoid types with a few leukocytes, at a five-day interval bloody fluid and roughening of the left ventricle, microscopically increased cellularity and vascularity with edema and congestion. Those rabbits surviving two injections and extending over periods of three and seven days showed macroscopically a similar lesion of the pericardium of the left ventricle with bloody fluid, and

microscopically a chronic plus and acute lesion. The last rabbit surviving six very large injections given in the same manner as those described previously in this series, showed at autopsy a muddy fluid with fibrous adhesions between parietal pericardium and left side of heart. Microscopically there was a much thickened cellular vascular pericardium with papilla formation over the left ventricle. It is evident that maximum doses of spartein followed by adrenalin, both given intravenously, produce the most marked pericardial lesion.

The mechanism of the production of this pericardial lesion appears to be simple. As the result of the use of spartein sulphate and adrenalin chlorid in the ways described above certain lesions of the myocardium associated with congestion are produced. In a certain number of instances this congestion is very marked, and associated with it there is exudation into the pericardial cavity, probably both serous and hemorrhagic in nature. This exudation is in part undoubtedly absorbed, but in a considerable number of animals absorption does not take place quickly and organization follows. This condition associated with cellular infiltration and proliferation in the pericardial layer itself gradually leads to a thickening of the pericardium with the formation of typical granulation tissue and adhesions, with as a final result the picture of a chronic proliferative pericarditis.

Carney Hospital  
252 Marlborough Street

#### STUDY XII EXPERIMENTAL ENDOCARDITIS PRODUCED BY SPARTEIN SULPHATE AND ADRENALIN CHLORID

HENRY A CHRISTIAN, M D, BOSTON

In various published studies of experimental cardiac lesions most attention has been given to lesions of the myocardium and the valves. No description of certain changes sometimes found in the endocardium lining the ventricular cavities has come to my notice, and yet these changes are not infrequent in rabbits that have received spartein sulphate and adrenalin chlorid given in different combinations;<sup>37</sup> they were found in fourteen of a group of fifty-one rabbits so treated, even though in each rabbit only a relatively small portion of the entire heart was submitted to microscopic study. For these reasons it seems desirable to describe the endocardial lesions found in rabbits after the almost simultaneous injection of spartein sulphate and adrenalin chlorid. For such a study there were available in the Laboratory of the Theory and Practice of Physic

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\*Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D C.

<sup>37</sup> For details of methods of dosage used in these experiments see series 2, 3, 4 and 5 in the paper by Walker on Experimental Myocarditis in this issue.

sections from hearts of rabbits that had been thus treated by Drs Walker and Dana for the purpose of studying other cardiac changes

The endocardial lesions to be described are more common in the left ventricle than in the right. Similar lesions, usually less developed, were noted sometimes in the auricles, but in only a few hearts were the auricles examined so that no statement as to the relative frequency of the lesion in auricles and ventricles can be given. Furthermore no exact statement as to relative frequency in the two ventricles is attempted for not all parts of either cavity were examined. Cross-sections were made through about half of the circumference of each ventricle and a portion of the interventricular septum a short distance below the auriculoventricular groove in all hearts and in some hearts sections in addition were made at right angles to the plane of the former. As far as can be judged from these the lesion is more commonly present or more fully developed in the left than in the right ventricle, thus corresponding to the distribution of myocardial lesions as described by Fleisher and Loeb,<sup>38</sup> and by Walker.<sup>37</sup> The lesion appears not to occur with any frequency if at all in the valves, at least the aortic and mitral valves were studied histologically and found normal in five of the fourteen rabbits that showed changes in the endocardium lining the cardiac cavities, and in five other rabbits with myocardial lesions.

The lesion found in these animals is entitled to be called endocarditis in that it is a progressive proliferative lesion, in sequence to injury to the endocardium associated with myocardial injury. It follows the use of certain drugs or chemicals given in combination. Whether they are caused mechanically as believed by Fleisher and Loeb for the myocardial lesions, whether they are a result of direct toxic action of the drugs, or whether they represent merely the extension to the endocardial surface of the myocardial lesion was not evident from the histological method of study here used.

The earliest change in the endocardium consists in a slight focal proliferation of the endothelium lining the cardiac cavity with an accompanying edema of the subendothelial connective tissue. Instead of the usual flattened type of endothelial cells you see more distinctly cuboidal cells with round or oval nuclei rather closely crowded together. The cells have increased in number and their nuclei are richer in chromatin.

This is well shown in Figure 25 from Rabbit 268, which received on December 17 spartan sulphate 0.025 gm subcutaneously, followed by adrenalin chlorid, 0.2 cc of a 1 to 1000 solution intravenously and in which these doses were repeated on December 20 and December 24, the animal dying on the same day as the last injections. In Figure 25 the extreme left-hand portion of the endocardium shows normal endothelium, while passing from this end the cells show

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38 Fleisher and Loeb THE ARCHIVES INT MED, 1909, III, 78, and 1910, VI, 427

increasingly well the changes described above. Where the endothelium shows most departure from the normal flat type the subendothelial connective tissue shows slight edema and very moderate cell infiltration (Figure 25).

Rabbit 272 received many more intravenous injections of smaller amounts of spartein sulphate and adrenalin chlorid, twenty-five in all, between December 17 and February 19, and showed a very similar lesion of the endocardium. Rabbit 296 was given spartein sulphate 0.035 gm intravenously, followed by adrenalin chlorid 0.2 cc of a 1-to-1000 solution, and was killed the next day. This animal showed a slight focal proliferation of the endothelium. Rabbit 270 had two intravenous injections of spartein sulphate 0.025 gm and adrenalin chlorid 0.2 cc of a 1-to-1000 solution three days apart and died four days after the last injection. It showed the endothelial proliferation already described and in addition in places there was considerable thickening of the endocardial layer so that instead of the normal endocardium there was a layer of young connective tissue quite cellular in character.

The endocardial thickening just described in Rabbit 270 represents a somewhat later stage of the endocarditic process in which the subendothelial connective tissue layer is thickened and cellular. The cellularity is made up of young connective tissue cells and infiltrating lymphocytes and plasma cells. Rabbit 279 with two doses five days apart of spartein 0.025 subcutaneously and adrenalin chlorid 1 to 1000 solution 0.2 cc intravenously showed several foci of cellular thickened endocardium as did Rabbit 79 after five doses between December 12 and April 24 (Figs 26, 27 and 28). Rabbits 280 and 292, treated very similarly to Rabbit 279 showed quite the same appearance, while Rabbit 283, treated very similarly to Rabbit 272, i. e., with numerous smaller doses, showed about the same degree of focal thickening, but without the cellularity found in the others. Rabbit 172 with four doses, both drugs subcutaneously, from October 30 to December 8, was very like Rabbit 283. Rabbit 165 after seven subcutaneous injections of spartein and adrenalin between October 27 and November 17 showed an area of thickened cellular endocardium. Rabbit 277 with four injections, spartein subcutaneously and adrenalin intravenously, January 5 to 17, and Rabbit 267, with eight intravenous injections of spartein and adrenalin December 17 to January 24, showed the same general process more extensive than in Rabbit 279.

Rabbit 282 with fourteen intravenous injections of spartein 0.007 to 0.008 gm and adrenalin 0.1 of a 1-to-1000 solution given at three-day intervals showed a more advanced process in which the endocardium was more extensively thickened, and this thickened endocardium was only moderately cellular. In Rabbit 266 the most extensive change was encountered. This animal was injected intravenously with spartein 0.020 to 0.025 gm, followed by adrenalin 0.2 cc at three-day intervals for five injections. The dose of spartein was then reduced to 0.018 gm and 0.0125 gm, respectively, for two more doses at three day intervals. The rabbit died shortly after the last, and the endocardium was found much thickened though not very cellular (Figs 29 and 30). In some places in this rabbit thickened endocardium was directly continuous with areas of newly formed connective tissue replacing muscle cells of the myocardium (Fig 31).

### *Summary*

In rabbits after the injection of spartein sulphate followed by adrenalin chlorid there develops a proliferative lesion of the endocardium lining the cardiac cavity. This is probably a quite frequent lesion usually accompanying myocardial and pericardial lesions, as it was found in fourteen of a series of fifty-one hearts, even though relatively very small portions of the endocardium were examined in each heart. The earliest change observed consisted in a slight proliferation of the endothelium

and edema of the subendothelial connective tissue. A more advanced stage shows proliferative thickening of the endocardium reaching a considerable degree in the most advanced lesion obtained in this series.

252 Marlborough Street

# STUDY XIII MYOCARDIAL LESIONS PRODUCED BY RENAL IRRITANTS (URANIUM, ARSENIC AND POTASSIUM BICHROMATE)

I CHANDLER WALKER, M.D., BOSTON

The lesions of the myocardium described in this paper are those lesions of the hearts taken from animals used in the experimental production of chronic nephritis. Dr. R. M. Smith, under the direction and supervision of Dr. H. A. Christian in the laboratory of the Department of the Theory and Practice of Physic, did this work on chronic nephritis. Mostly rabbits were used, but a few guinea-pigs were tried, although not very successfully for the kidney work, since they would not survive sufficiently large amounts of the drugs. An aqueous solution of uranium nitrate in doses varying from 0.0005 to 0.005 gm., an aqueous solution of potassium bichromate in varying amounts of a 1 per cent and a 5 per cent solution and arsenic in the form of Fowler's solution in 8 and 10 minim doses were used. All drugs were used by subcutaneous injection and, in addition, in a few instances, Fowler's solution was given by the stomach-tube. For a detailed description of the methods employed, the results obtained and the protocols, etc., I refer to Dr. Smith's paper on "Experimental Chronic Nephritis," this issue. The hearts of these animals are considered as controls to those used in the experimental production of myocarditis by spartem sulphate and adrenalin chlorid. In this paper only that portion of each protocol which deals with a pathological change in the circulatory system will be mentioned.

A series of thirteen rabbits of varying weights were injected subcutaneously with 0.001 and 0.002 gm. of uranium nitrate at varying intervals.

Rabbit 259, weight 1500 gm., was injected subcutaneously with 0.002 gm. of uranium nitrate every three or four days, in all, four injections were given in twenty one days, and the rabbit died three days after the last injection. Nothing macroscopically abnormal was noted at autopsy. Microscopically, there were present in the myocardium foci of young connective tissue cells, these foci were quite extensive and very frequent, and the muscle was somewhat replaced by them.

Rabbit 260, weight 1575 gm., No. 261, weight 1760 gm., No. 264, weight 2070 gm. were all injected subcutaneously every three or four days with 0.002 gm. of uranium nitrate for fourteen times, extending over a period of two months. At autopsy macroscopically nothing pathological was found. Microscopically,

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the myocardium of each rabbit showed foci of young connective tissue cells with fibrils, lymphoid and plasma cells. These foci were fairly extensive and frequent. This picture was very similar to that in Rabbit 259 previously described, except that some foci seemed to be made up of younger connective tissue cells and thus more recent lesions, while other foci appeared older and more advanced. These foci more or less replaced the muscle.

Rabbits 207, 208, 221 and 227, weighing respectively 1530, 1740, 1435, 1460 and 1345 gm, were injected subcutaneously with 0.002 gm of uranium nitrate every three or four days during a period of four months, thirty injections in all. Rabbits 207 and 208 were killed four weeks after the last injection, and at autopsy nothing grossly pathological was noted with the exception of an excess in the amount of fluid in the body cavities of Rabbit 208. The fluid of the pericardial cavity of Rabbit 208 appeared to be considerably increased, and the heart was large. Microscopically, the myocardium of Rabbit 207 was markedly congested with quite marked infiltration with lymphoid cells, especially the subpericardial myocardium. In addition there was a moderate increase of young connective tissue and lymphoid cells, diffusely, and in small foci throughout the myocardium. The myocardium of Rabbit 208 showed a moderate diffuse young connective tissue and lymphoid cell infiltration. In addition, at the base of the left ventricle there was a large area of young connective tissue cells with fibrils, large numbers of leukocytes and lymphocytes. In this area the muscle which appeared to be hypertrophied, was more or less replaced by the above cells and the walls of the blood vessels at this place were infiltrated with similar cells. Rabbit 209 was killed six weeks after the last injection. At autopsy there was much fluid in all the body cavities, and the heart was large. Microscopically there was an extremely slight increase of young connective tissue cells in small diffuse foci. Rabbit 221 was killed three days after the last injection. The organs appeared normal at autopsy. Microscopically there was marked congestion and some edema of the myocardium with a slight amount of young connective tissue, lymphoid and leukocyte cell infiltration, diffusely situated, but most marked in the subpericardial myocardium. Rabbit 227 died during an edema experiment, six weeks after the last injection. At autopsy the only thing pathological noted was a large amount of a free, very bloody fluid in the abdominal cavity. Microscopically there was an extremely slight increase of young connective tissue cells in small diffuse foci.

Rabbit 226, weight 1310 gm, was injected subcutaneously with 0.002 gm of uranium nitrate every three or four days for seven injections. The rabbit died two days after the last injection. At autopsy nothing abnormal was noted except that the aorta was very brittle, parchment-like and crumbled on pressure. Microscopically a similar picture to that in Rabbit 227 was seen.

Rabbits 124, 129 and 130, weighing respectively 2,000, 1,520 and 2,000 gm, were each injected subcutaneously with 0.001 gm of uranium nitrate daily for eight days, after which the amount of uranium nitrate was increased to 0.002 gm, and injected subcutaneously daily for nine more times. After this 0.002 gm of uranium nitrate was injected subcutaneously every three or four days for twenty-five injections. Altogether these three rabbits received forty-two injections in five and a half months. Rabbit 130 was killed three days after the last injection, Rabbit 129 ten days, and Rabbit 124 was killed four weeks after the last injection. At autopsy nothing pathological was seen in any animal. Microscopically Rabbit 130 showed slight congestion and very slight young connective tissue and lymphoid cell increase, diffusely situated in the myocardium. The myocardium of Rabbit 129 was congested in places, and one small focus of young connective tissue and lymphoid cells was noted in the wall of the left ventricle. Rabbit 124, microscopically showed very slight young connective tissue and lymphoid cell infiltration throughout the myocardium with slight congestion, which was more marked in the subpericardial myocardium. In addition, the walls of the blood-vessels appeared to be infiltrated with young connective tissue cells.

Therefore, to summarize the findings in this series of thirteen rabbits, three rabbits which were injected daily for seventeen days and every three or four days for twenty-five times, showed only a very slight increased cellularity of the myocardium. Four other rabbits injected a less number of times showed a similar picture. The remaining six rabbits showed a fairly marked lesion of the myocardium, chiefly foci of young connective tissue and lymphoid cells, which replaced to a more or less extent the muscle of the myocardium. However, in none of these rabbits was the lesion very marked, or very destructive, and in none was it extensive.

A second series of twenty-two rabbits of varying weights was injected subcutaneously with 0.005 gm of uranium nitrate at three-week intervals, this interval having been found to give the most satisfactory lesions in the kidneys.

Rabbits 198, 199 and 200, weights respectively 1190, 1140 and 1190 gm, were injected subcutaneously with 0.005 gm of uranium nitrate and all died five days after being injected. At autopsy all three rabbits had a large amount of free bloody fluid in the abdominal, thoracic and pericardial cavities. Microscopically there was congestion of the subpericardial myocardium with edema, most marked in Rabbit 199 and less marked in Rabbit 200. In addition, there was a slight diffuse infiltration of the myocardium with young connective tissue and lymphoid cells and leukocytes. In Rabbit 198 the cellular increase was more marked than in Rabbits 199 and 200.

Rabbits 246, weight 1520 gm, and 251, weight 1690 gm, were injected the same as the ones just described, and these died seven days after being injected. At autopsy both rabbits had an excess amount of fluid, straw-colored, in the abdominal cavity. Microscopically both rabbits showed a slight diffuse young connective tissue and lymphoid cell infiltration of the myocardium.

Rabbit 128, weight 1330 gm, was injected subcutaneously with 0.005 gm of uranium nitrate, and at the end of three weeks this was repeated. The rabbit died twelve days after the second injection. At autopsy nothing pathological was noted. Microscopically there was congestion of the myocardium with very slight increase of young connective tissue and lymphoid cells, and very slight thickening of the walls of the blood vessel. In addition, the myocardium of the left ventricle at the base of the heart contained a large area of cells of the young connective tissue and lymphoid cell types. In this area the muscle was almost replaced by the cellularity, only shreds of muscle were evident.

Rabbit 190, weight 1390 gm, was injected the same as No. 128, except that it got one more injection, and died eleven days after the last, or third injection. At autopsy the aorta was stiff and like parchment, and the heart muscle appeared mottled with whitish specks. Microscopically there was a very marked patchy infiltration of the myocardium with young connective tissue cells, and fine connective tissue fibrils. These areas of cellularity were quite extensive and frequent and replaced the muscle to a more or less extent. There was an increase of young connective tissue about the walls of the blood-vessels, which were slightly thickened.

Rabbits 247, 248, 249, 250 and 252, weighing respectively 1430, 1720, 2080, 2380 and 2480 gm, were all injected subcutaneously with 0.005 gm of uranium nitrate five times, with three-week intervals between the injections, extending over a period of three months. These rabbits were killed respectively six weeks, four weeks, three days, seven weeks, and six weeks after the last injection. At autopsy nothing pathological was noted in any of the rabbits, except in Rabbit 252, which had a large, pale and flabby heart, and there was a slight excess of fluid stained with blood in the abdominal, thoracic and pericardial cavities.

Microscopically Rabbit 247 showed foci of young connective tissue cells with fibrils replacing the muscles to a slight extent. In Rabbits 248 and 250 the myocardium was very slightly infiltrated with young connective tissue and lymphoid cells diffusely situated. Microscopically the myocardium of Rabbits 249 and 252 showed a slight diffuse increase of young connective tissue and lymphoid cells. In addition there was an area in the myocardium of the left ventricle where young connective tissue cells with fibers invaded the already hypertrophied muscle. The muscle looked like a network on which the new young tissue was growing.

Rabbits 189, 191, 192, 193, 194, 195, 196 and 197, weighing respectively 1390, 1490, 1470, 2500, 1280, 1170, 1215, and 1145 gm, were all injected subcutaneously with 0.005 gm of uranium nitrate seven times at three-week intervals during a period of four months. These rabbits were killed at varying intervals, four weeks, two weeks, two days, four weeks, six weeks, four weeks, six weeks, and seven weeks respectively after the last injection. At autopsy the heart muscle of Rabbit 189 was of a grayish color and cut with resistance. The other rabbits showed no pathological change of the circulatory system. Microscopically the myocardium of Rabbit 189 was rather markedly infiltrated with young connective tissue and lymphoid cells, also there were areas where the hypertrophied muscle was replaced by older fibrous tissue through which young connective tissue and lymphoid cells were scattered. The subpericardial myocardium was congested and there was a diffuse cellularity of the two above-mentioned types. The walls of the blood-vessels seemed to be thickened and infiltrated with young connective tissue cells. The myocardium of Rabbits 191, 192 and 193 was very slightly infiltrated diffusely with young connective tissue cells and the muscle was somewhat hypertrophied. The last rabbit, No 193, had a more marked cellular increase than the two former. Rabbit 194 showed a very slight diffuse young connective tissue and lymphoid cell increase. The myocardium of Rabbit 195 was congested, edematous, quite markedly infiltrated with lymphoid cells, a few leukocytes and young connective tissue cells. Rabbits 196 and 197 showed a similar picture. There was a very slight diffuse increased cellularity with occasional foci of young connective tissue and lymphoid cells, also mild congestion and slight muscle hypertrophy.

Rabbit 178, weight 1580 gm, was injected subcutaneously like the above rabbits for six times and killed nine weeks after the last injection. Microscopically there was slight diffuse young connective tissue and lymphoid cell increase with slight hypertrophy of the muscle of the myocardium.

Rabbits 177 and 187, weighing respectively 1250 and 1360 gm, were injected subcutaneously with 0.004 gm of uranium nitrate six times at three-week intervals and were killed four and nine weeks after the last injection. The myocardium of Rabbit 177 showed a very slight diffuse young connective tissue and lymphoid cell increase. The walls of the blood-vessels were thickened and the intimal cells appeared to be proliferated. The myocardium of Rabbit 187 showed a more marked lesion. The young connective tissue cells had fibrils, and these had invaded degenerated muscle fibers, and the new tissue more or less replaced the muscle. A few lymphoid cells were noted.

In this series of twenty-two rabbits, the myocardium of ten rabbits showed only a very slight increased cellularity. The myocardium of the remaining twelve rabbits showed a fairly marked increased cellularity of the young connective tissue and lymphoid cell types, situated diffusely and in foci, which caused degeneration of the muscle and more or less replaced it.

A third series consisted of guinea-pigs of varying weights injected subcutaneously with varying amounts of uranium nitrate, ranging from

0.0005 gm to 0.003 gm, at varying intervals. Nothing grossly pathological was found in these animals.

Guinea-Pig 175, weight 475 gm, was injected subcutaneously with 0.001 gm of uranium nitrate and died four weeks later. Microscopically there was quite a marked diffuse increased cellularity of the young connective tissue and lymphoid cell types, with slight congestion of the myocardium. Also these cells were present in small foci.

Guinea-Pig 140, weight 440 gm, was injected subcutaneously with 0.001 gm of uranium nitrate and this was repeated every three weeks for eight injections. The guinea-pig died ten days after the last injection. Microscopically the myocardium showed a similar picture to Guinea-Pig 175.

Guinea-Pigs 139 and 142, weights 685 and 560 gm, were injected subcutaneously with 0.0005 gm of uranium nitrate every other day for ten injections. Then the amount of uranium was increased to 0.001 gm and Guinea-Pig 142 died three weeks after this injection. Guinea-Pig 139 survived eight injections of 0.001 gm each at three week periods, and was killed ten days after the eighth injection. Microscopically the myocardium of each guinea-pig showed a similar picture, namely, a slight congestion and a diffuse slight young connective tissue increase with occasional foci of young connective tissue and lymphoid cells. The walls of the blood-vessels appeared to be slightly thickened.

Guinea-Pigs 186 and 241, weights 390 and 485 gm, were injected subcutaneously with 0.001 gm of uranium nitrate and this was similarly repeated four times with three-week intervals between each injection. Guinea-Pig 186 died ten days after the last injection, and Guinea-Pig 241 died four days after the last injection. Microscopically the myocardium of Guinea-Pig 186 was slightly congested and was infiltrated with foci of young connective tissue and lymphoid cells. The walls of the blood-vessels appeared considerably thickened and infiltrated with young connective tissue cells. The myocardium of Guinea Pig 241 was diffusely infiltrated with young connective tissue and lymphoid cells. This was most marked in the subpericardial myocardium. The walls of the blood vessels were thickened with an increase of young connective tissue cells.

Guinea-Pig 176, weight 550 gm, was injected subcutaneously with 0.001 gm of uranium nitrate six times at three week intervals, and was killed ten days after the last injection. Microscopically the myocardium was considerably congested and moderately infiltrated with lymphoid and young connective tissue cells and a few leukocytes.

Guinea-Pig 185, weight 670 gm, was injected subcutaneously with 0.002 gm six times at three week intervals and was killed ten days after the last injection. Microscopically there was a slight diffuse young connective tissue and lymphoid cellularity, although the same types of cells appeared in small scattered foci. The above cellularity was most marked in the subpericardial myocardium. There was considerable congestion. The walls of the blood vessels were slightly thickened.

Guinea-Pig 229, weight 400 gm, was injected subcutaneously with 0.001 gm of uranium nitrate five times at three-week intervals and the guinea pig was killed five weeks after the last injection. Microscopically the myocardium was markedly congested and considerably infiltrated diffusely with young connective tissue cells. The muscle appeared to be hypertrophied. The vessel walls were somewhat thickened.

Guinea-Pig 188, weight 450 gm, was injected subcutaneously with 0.003 gm of uranium nitrate, and the guinea-pig died six days later. The myocardium, microscopically, showed congestion and a slight diffuse young connective tissue cellularity.

This series of ten guinea-pigs received a similar amount of uranium nitrate in proportion by weight as did the rabbits in the previous series,

and they likewise showed a similar lesion of the myocardium, which was possibly more marked, and more extensive in proportion to their weights than the previous series of rabbits showed. The thickening of the walls of the blood-vessels was more striking and more constant in this series.

Another series of rabbits were experimented on with Fowler's solution, which was injected subcutaneously in 8 and 10 minims doses, and also was given in similar amounts, with equal parts of water, by stomach tube. Fourteen rabbits were used in this series.

Rabbit 121, weight 2250 gm, was injected subcutaneously daily with 4 minims of Fowler's solution twice, 7 minims once, and after this with 10 minims daily for nine times. The injections were then suspended for one month, on account of severe sloughing of the abdominal wall at the site of the previous injections, and also because the urine examination showed that the rabbit had a marked lesion of the kidneys. At the end of a month 10 minims of Fowler's solution with equal parts of water were given by the stomach tube and this was repeated twice every other day. The rabbit died three days after the last dose. Altogether the rabbit received twelve subcutaneous injections daily and three doses by the stomach-tube. At autopsy the heart was very large. Microscopically the myocardium was congested and there was one area of hemorrhage at the base of the left ventricle near the septum. The subpericardial myocardium appeared to be recently congested.

Rabbit 138, weight 2730 gm, was injected subcutaneously with 10 minims of Fowler's solution, and this was repeated two days later. Three weeks later 10 minims of Fowler's solution was given by the stomach-tube. This was repeated three days later, and again five days later. The rabbit died two days after the third dose by the stomach tube. At autopsy the heart seemed large. Microscopically in the myocardium there were areas of fibrous tissue replacing the muscle, which was left as little fragments scattered through the fibrous tissue. In other areas there was infiltration with young connective tissue and lymphoid cells. The papillary muscles were very fibrous.

Rabbit 235, weight 2520 gm, was given 10 minims of Fowler's solution by the stomach-tube. This was repeated six times at weekly periods and three times at ten-day intervals. The rabbit was killed nine weeks later. The heart was large. Microscopically there were foci of young connective tissue cells replacing the muscle of the myocardium.

Rabbits 236 and 238, weighing 1920 and 1730 gm, were each given 8 minims of Fowler's solution by stomach tube and this was repeated every seven days for six times, and after this every ten days for three more times. The rabbits were killed six and eight weeks respectively after the last dose. At autopsy nothing grossly pathological was found. Microscopically Rabbit 236 showed an extremely slight diffuse and an occasional small focus of young connective tissue and lymphoid cellularity. Rabbit 238, microscopically, showed a slight diffuse young connective tissue cell infiltration of the myocardium, with muscle hypertrophy, and also very small foci of lymphoid cells. The walls of the blood-vessels were thickened and there was capillary congestion.

Rabbit 132, weight 2050 gm, was injected subcutaneously with 10 minims of Fowler's solution seven times in ten days and the rabbit died on the eleventh day. Nothing pathological was noted at autopsy. Microscopically there was a very slight young connective tissue cell increase diffusely with slight muscle hypertrophy and congestion of the myocardium, also there was a slight amount of old fibrous tissue infiltrated with young connective tissue cells, and a few small foci of these cells were scattered through the myocardium. The walls of the blood vessels were thickened.

Rabbit 233, weight 1600 gm, was injected subcutaneously with 8 minims of Fowler's solution, and repeated seven times at weekly intervals and three

times more at ten-day periods, extending over a period of three months altogether. Six weeks after the last injection the rabbit was killed. At autopsy nothing pathological was noted. Microscopically there was congestion and a slight diffuse cellularity of the young connective tissue and lymphoid cell types, also these same cells were in foci. In addition, there were areas of young connective tissue cells with fibrils replacing the already hypertrophied muscle. The walls of the blood-vessels were thickened and infiltrated with young connective tissue cells.

Rabbits 239 and 243, weights 2250 and 2280 gm, were injected subcutaneously with 10 minims of Fowler's solution. In Rabbit 239 this was repeated every seven days for three times and the rabbit died seven days after the last injection. In Rabbit 243 this was repeated twice at weekly intervals and the rabbit died two days after the last injection. At autopsy Rabbit 239 showed no pathological lesion, but Rabbit 243 had an excess of fluid in the pericardium and the heart was very large. Microscopically both rabbits showed a similar lesion of the myocardium. There was a slightly increased cellularity, both diffusely and in small foci of the young connective tissue and lymphoid cell types, with moderate congestion and muscle hypertrophy. The walls of the blood-vessels were thickened.

Rabbits 253, 254, and 255, weighing 2250, 1950, and 2180 gm respectively, were each injected subcutaneously with 10 minims of Fowler's solution, and this was repeated six times at ten day intervals. The rabbits were killed eight and six weeks after the last injection. At autopsy nothing pathological was found. Microscopically Rabbits 253 and 254 showed a very slight young connective tissue cell increase of the myocardium. Rabbit 255 showed only marked congestion of the myocardium.

Rabbits 234 and 237, weighing 2470 and 1950 gm, were injected subcutaneously with 10 minims of Fowler's solution, repeated six times at weekly intervals and three times more at ten day intervals. One rabbit was killed eight and the other six weeks after the last injection. At autopsy nothing pathological was noted. Microscopically Rabbit 234 had a slight diffuse young connective tissue and lymphoid cellularity of the myocardium with muscle hypertrophy. The walls of the blood-vessels were slightly thickened. The myocardium of Rabbit 237 showed young connective tissue and lymphoid cells diffusely and in foci with slight hypertrophy of the muscle.

In this series of fourteen rabbits all showed a more or less increased cellularity of the myocardium diffusely or in foci or both. In two rabbits there was only congestion of the myocardium, in six others a slight cellularity of the myocardium with slight hypertrophy of the muscle. In the remaining six rabbits the cellularity was more marked, but not very extensive. In all cases the walls of the blood-vessels seemed to be thickened. The cellularity was of the young connective tissue and lymphoid cell types.

Another series consisting of seven guinea-pigs were injected subcutaneously with varying doses of potassium bichromate in a 1 and a 5 per cent aqueous solution.

Guinea-Pigs 136 and 137, weights 475 and 490 gm, were injected subcutaneously with 2 minims of a 5 per cent solution of potassium bichromate. The former died four days and the latter twelve days after the injection. At autopsy no pathological lesion was noted. Microscopically both guinea-pigs showed a similar lesion of the myocardium. There was marked congestion and a slight diffuse young connective tissue and lymphoid cellularity, which was most marked about the walls of the blood-vessels. There were areas where the muscle appeared hypertrophied and other areas where it is degenerated, the muscle cells having

swollen and faintly stained nuclei. The walls of the blood-vessels were thickened, and infiltrated with young connective tissue cells, and the cells of the intima appeared to be proliferating.

The remaining five guinea-pigs of this series although they received different amounts of the potassium bichromate and at different intervals, all showed a similar lesion and consequently all will be taken together.

Guinea-Pig 179, weight 480 gm, was injected subcutaneously with 2 minims of a 1 per cent solution of potassium bichromate. This was repeated three days later, again in five days and nine days. Eleven days later the dose was increased to four minims, and two days after this to 8 minims, which was repeated four times at weekly periods and four more times at three-week intervals. Thus the guinea-pig received four 2-minim doses, one 4-minim and nine 8-minim injections. The guinea-pig was killed ten days after the last injection. Guinea-Pig 180, weight 465 gm, was injected similarly, including the second 8-minim dose, after which it died. Guinea-Pig 181, weight 835 gm, was injected subcutaneously with 2 minims of a 5 per cent solution of potassium bichromate, and this was repeated six days later, and again nine days later. On the eleventh day, that is, two days after the last injection, the amount of potassium bichromate was changed to 5 minims of a 1 per cent solution and this was injected twice with two days intervening. Two days later again the dose of potassium bichromate was increased, this time to 15 minims of a 1 per cent solution, and was injected six times at weekly intervals and three times at three-week intervals. The guinea-pig was killed eight weeks after the last injection. Guinea-Pig 183, weight 400 gm, was injected subcutaneously with 5 minims of a 1 per cent solution of potassium bichromate three times in ten days. After this the amount of bichromate was increased to 8 minims of the 1 per cent solution and was injected subcutaneously eight times at weekly periods and two times at three week intervals. The guinea-pig was killed ten days after the last injection. Guinea-Pig 184, weight 390 gm, was injected subcutaneously with 1 minim of a 1 per cent solution of potassium bichromate six times in twelve days and with 8 minims of a 1 per cent solution two times in three weeks. The guinea pig died one day after the last injection. At autopsy none of these guinea-pigs showed a pathological lesion of the heart. Microscopically they all showed a very similar lesion of the myocardium. There was marked congestion and a slight diffuse cellularity of the young connective tissue and lymphoid cell types. Also these cells appeared in rather extensive foci, and were more noticeable about the blood-vessels. The walls of the blood vessels were thickened and were infiltrated with the same types of cells. In Guinea-Pigs 180 and 184 this cellularity was less marked than in the two other guinea-pigs.

This series showed a rather more marked cellularity of the myocardium than any previous series, although the lesion in none of these guinea-pigs was very extensive or destructive.

The last series consisted of seventeen rabbits of varying weights injected subcutaneously with varying amounts of potassium bichromate in an aqueous solution at varying intervals.

Rabbits 131 and 133, each weighing 1900 gm, were injected subcutaneously with 1 cc of a 5 per cent solution of potassium bichromate, and they died five and six days later, respectively. At autopsy no pathological lesion was found. Microscopically the myocardium of Rabbit 131 showed a very slight cellularity of the young connective tissue and lymphoid cell types diffusely and in foci. The walls of the blood-vessels were slightly thickened and infiltrated with young connective tissue cells. Rabbit 133 showed a similar picture in the myocardium, except that there was in addition congestion and plasma cells in the foci and more degeneration of the muscle cells which had lost the cross-striations.



Rabbit 125, weight 1200 gm, was injected subcutaneously with 1 cc of a 5 per cent solution of potassium bichromate, the injection being repeated on the following day. The rabbit died on the third day. Nothing pathological was noted at autopsy. Microscopically there were areas of old fibrous tissue infiltrated with young connective tissue cells, also foci of these young cells which replaced the muscle cells.

Rabbit 182, weight 2170 gm, was injected subcutaneously with 0.75 cc of a 5 per cent solution of potassium bichromate. The rabbit died two weeks later. At autopsy nothing pathological was noted. Microscopically there was congestion and numerous and extensive foci of young connective tissue cells with fibrils, lymphoid cells and a very few leukocytes.

Rabbits 134 and 135, weighing 1840 and 1880 gm, were each injected subcutaneously with 0.5 cc of a 5 per cent solution of potassium bichromate. This was repeated eight days later, and thereafter 21 minims of a 1 per cent solution of potassium bichromate was injected subcutaneously at three week intervals for four injections. Both were killed eight weeks after the last injection. At autopsy nothing pathological was found. Microscopically both rabbits showed a similar lesion of the myocardium. There was a slight diffuse young connective tissue and lymphoid cell increase with moderate congestion. In addition, there were foci of young connective tissue, lymphoid cells, and plasma cells. These foci were quite extensive, and replaced the muscle cells. The myocardium of Rabbit 135 had a slightly more extensive lesion than did Rabbit 134. In both the walls of the blood-vessels were thickened.

Rabbits 222, 223, 224, 225, and 231, weighing respectively 1300, 1530, 1730, 1700, and 1330 gm, were each injected subcutaneously with 21 minims of a 1 per cent solution of potassium bichromate. This was repeated every three weeks for four more injections. The rabbits were killed respectively ten, three, ten, nine and eight weeks after the last injection. At autopsy only Rabbit 225 showed a pathological change, and this was a straw colored fluid in the abdominal cavity. Microscopically Rabbits 222, 224, and 225 had a similar lesion of the myocardium. This was a slight diffuse young connective tissue cellularity and also foci of these cells with fibrils scattered throughout the myocardium with more or less replacement of the muscle cells by these foci. The walls of the blood vessels were thickened. The other two rabbits, Nos 223 and 231, showed only a very slight diffuse young connective tissue cellularity of the myocardium.

Rabbits 244, 245, 257, and 258, weighing respectively 2380, 2050, 2330 and 3310 gm, were each injected subcutaneously with 21 minims of a 1 per cent solution of potassium bichromate four times at three-week intervals. The rabbits were killed eight, one, five, and nine weeks respectively after the last injection. At autopsy the only pathological lesion found was in Rabbit 245, whose aorta was stiffened and sclerosed. In Rabbit 257 the visceral pericardium was covered with a very slight fibrinous film, and the heart of Rabbit 258 was large. Microscopically the myocardium of Rabbit 244 showed no lesion. The myocardium of Rabbit 245 showed a slight diffuse young connective tissue and lymphoid cellularity. In addition in the center of the myocardium of the left ventricle there was an area of young fibrous tissue invading and replacing the muscle. The walls of the blood-vessels were infiltrated with young connective tissue cells. The myocardium of Rabbits 257 and 258 showed a very slight diffuse young connective tissue cellularity, with a very few lymphoid cells.

Rabbit 228, weight 1310 gm, was injected subcutaneously with 21 minims of a 1 per cent solution of potassium bichromate three times at three week intervals, and the rabbit died three days after the last injection. At autopsy there was considerable blood stained fluid in the abdominal cavity. Microscopically the myocardium showed an increased cellularity of the young connective tissue and lymphoid types, both in foci and diffusely.

Rabbits 262 and 263, weights 1550 and 2000 gm, were each injected subcutaneously with 21 minims of a 1 per cent solution of potassium bichromate twice with three weeks intervening between the two injections. The rabbits were killed



eleven and twelve weeks after the last injection. At autopsy no pathological lesion was found. Microscopically the myocardium of each rabbit showed small clumps or beginning foci of young connective tissue and lymphoid cells.

As did the previous series, this series showed a slight cellularity of the young connective tissue and lymphoid cell types in foci and diffusely. In no rabbit was the lesion at all extensive.

### *Summary*

Although practically all these animals showed a more or less increased cellularity of the myocardium, it was extremely slight in many, and in no animal was the cellularity marked. Whereas, in the series in which spartein sulphate and adrenalin chloride were used intravenously and in which the spartein was injected subcutaneously followed intravenously by adrenalin, all the rabbits showed a considerable increased cellularity, and in some there was a considerable connective tissue proliferation. Also the extent of the lesion was in proportion to the number of injections in the spartein series. But in the series just described in this paper the number of injections seemed to play a small part in the extensiveness of the lesion.

Carney Hospital

### STUDY XIV PERICARDIAL LESIONS PRODUCED BY RENAL IRRITANTS (URANIUM NITRATE, ARSENIC AND POTASSIUM BICHROMATE)

I CHANDLER WALKER, M D, BOSTON

During the past winter, 1910, Dr R M Smith, at the suggestion and under the supervision of Dr H A Christian, did some experimental work on chronic nephritis. The drugs used were an aqueous solution of uranium nitrate, arsenic in the form of Fowler's solution, and potassium bichromate in aqueous solution. These drugs were used subcutaneously in various doses and at various intervals, and in addition, the arsenic was given by stomach tube. The majority of animals used were rabbits, and a few guinea-pigs. For a more detailed description and the results obtained I refer to Dr Smith's paper. The work was carried on in the Department of Theory and Practice of Physic at the Harvard Medical School. This paper is a description of the lesions of the pericardia that occurred in Dr Smith's experiments, and these may be considered a control to the experiments in which spartein sulphate and adrenalin chloride were used to produce pericarditis.

One series of thirteen rabbits of varying weights were injected subcutaneously with 0.001 gm and 0.002 gm of uranium nitrate at various intervals.

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In this series, although all the rabbits showed either an acute or a chronic lesion of the kidneys, none showed any lesion of the pericardium.

Another series of twenty-one rabbits of varying weights were injected subcutaneously with 0.005 gm of uranium nitrate at three-week intervals, which interval was found to produce the most satisfactory kidney lesion. In this series thirteen rabbits showed no lesion of the pericardium, whereas eight rabbits did have a lesion of the pericardium although it was not marked.

Rabbits 198, 199 and 200, weighing respectively 1190, 1140, and 1190 gm, were injected subcutaneously with 0.005 gm of uranium nitrate, and all died five days after injection. Macroscopically, no lesion of the pericardium could be made out. Microscopically their pericardia showed congestion which was more marked in some places than in others.

Rabbit 251, weight 1690 gm, was injected once in the same manner with the same drug, and it died seven days later. Macroscopically there was no lesion, but microscopically the pericardium showed slight infiltration with young connective tissue and lymphoid cells.

Rabbits 194, weight 1280 gm, 195, weight 1170 gm, and 196, weight 1215 gm, were injected subcutaneously with 0.005 gm of uranium nitrate, and this was repeated at three-week intervals for six times more, the rabbits being killed four and six weeks after the last injection. Macroscopically there was no pericardial lesion. Microscopically Rabbits 194 and 195 showed a slight increased cellularity of the young connective tissue and lymphoid cell types. Rabbit 196, microscopically, showed a slight increased cellularity throughout the pericardium, like the two former rabbits and in addition the pericardium at the base of the left ventricle was rather markedly infiltrated with lymphoid cells and young connective tissue, which in one place extended down into the subpericardial myocardium to form a fairly large patch of loose fibrous tissue infiltrated with young connective tissue and lymphoid cells with a few red blood cells and leukocytes. The muscle is degenerated and is replaced by this patch of tissue.

Rabbit 178, weight 1580 gm, was injected subcutaneously six times at three-week periods with 0.005 gm of uranium nitrate, and was killed nine weeks after the last injection. Macroscopically the pericardium showed no lesion. Microscopically there was a slight increase of young connective tissue cells with increased vascularity at the juncture of the pericardium and the myocardium.

The remaining rabbits of this series showed no lesion of their pericardia.

Thus it is seen that of twenty-one rabbits all injected similarly, and all of which showed either acute or chronic lesions of both of their kidneys, only eight rabbits had a lesion of their pericardium, and this lesion was only slight in each rabbit, and it was not confined to any special number of injections or to any special time limit, although four of the rabbits showing a lesion, namely, congestion only, received only one injection and died a few days later. The other four rabbits having a lesion of the pericardium were injected six and seven times, and this lesion was only a slight increased cellularity of the young connective tissue and lymphoid cell types.

In a third series guinea-pigs of varying weights were injected subcutaneously with varying doses of uranium nitrate at varying intervals of

time In all, ten guinea-pigs were used and all showed a more or less marked lesion of their pericardia microscopically, but nothing macroscopically

Guinea-Pig 175, weight 475 gm, was injected subcutaneously with 0.001 gm of uranium nitrate, and died four weeks later. Microscopically there was proliferation of the pericardial cells.

Guinea-Pigs 140, weight 440 gm, 186, weight 390 gm, and 176, weight 550 gm, were all injected subcutaneously with 0.001 gm of uranium nitrate, which was repeated at three-week intervals for eight, five and six times in each rabbit respectively. Guinea-Pig 140, receiving eight injections, and killed ten days after the last injection, showed foci of young connective tissue and lymphoid cells at the juncture of the pericardium and the myocardium. In Guinea-Pig 186, which was injected five times, and died ten days after the last injection, the pericardium showed moderate congestion and a fairly marked increase of young connective tissue and lymphoid cells at the juncture of the pericardium and the myocardium. Guinea-Pig 176 received six injections and was killed ten days after the last injection. There was a slight young connective tissue and lymphoid cell increase.

Guinea-Pigs 139, weight 685 gm, and 142, weight 560 gm, were injected subcutaneously with 0.0005 gm of uranium nitrate every other day for ten injections, and after this the uranium was increased to 0.001 gm. Guinea Pig 142 died three weeks later, and the pericardium was slightly thickened with some young connective tissue cell increase, a few plasma cells, and a few red blood cells also were present. The other, Guinea-Pig 139, survived eight injections of 0.001 gm at three-week intervals, and was killed ten days after the eighth injection. The pericardium showed only congestion and edema.

Guinea-Pigs 229, weight 400 gm, and 241, weight 485 grams, were injected subcutaneously with 0.001 gm of uranium nitrate, which was repeated in 229 for three times and the animal was killed five weeks after the fourth injection. In Guinea-Pig 241 the drug was repeated four times, when the animal died four days after the fifth injection. In Guinea-Pig 229 the pericardium was slightly thickened with an increase in the young connective tissue and lymphoid cells, and in addition, a few plasma cells were present. Guinea-Pig 241 showed the same kind of cells, but in foci scattered throughout the pericardium.

Guinea-Pig 185, weight 670 gm, was injected subcutaneously with 0.002 gm of uranium nitrate, repeated five times at three week intervals, and was killed ten days after the sixth injection. There was quite marked congestion of the pericardium, and marked young connective tissue and lymphoid cell increase at the juncture of the pericardium and the myocardium.

Guinea-Pig 188, weight 450 gm, was injected subcutaneously with 0.003 gm of uranium nitrate, and died six days later, showing thickening of the pericardium in places where there was considerable young connective tissue and lymphoid cell increase with numerous plasma cells.

The guinea-pigs which got a slightly larger dose of uranium nitrate in proportion to weight than the rabbits showed a slightly more marked lesion and this lesion was more constant.

A series of rabbits, fourteen in all, were experimented on with arsenic in the form of Fowler's solution. Three rabbits received the arsenic by stomach-tube, a dose of 8 or 10 minims in as much water. Two rabbits were injected subcutaneously several times, and afterward it was given by stomach tube. Nine rabbits were injected subcutaneously only, the subcutaneous dose in all rabbits being 10 minims undiluted, with the exception of one rabbit, which got 8 minims.

Rabbit 213, weight 2280 gm, was injected subcutaneously with 10 minims of Fowler's solution. This was repeated at seven day intervals between the doses for two times, and the rabbit died two days after the last or third injection. At autopsy the pericardium was filled with a colorless fluid. Nothing was made out macroscopically. Microscopically there were areas of marked congestion, and an occasional lymphoid and young connective tissue cell.

Rabbit 239, weight 2250 gm, was injected subcutaneously with 10 minims of Fowler's solution for four times, with seven day intervals between the injections. This rabbit died seven days after the last injection. There was nothing abnormal macroscopically. Microscopically there was very slight young connective tissue and plasma cell infiltration with slight congestion and edema of the pericardium.

Rabbits 254, weight 1950 gm, and 255, weight 2180 gm, were injected subcutaneously with 10 minims of Fowler's solution at ten-day intervals. Each rabbit received seven injections. The former died two days after the last injection; the latter was killed six weeks later. Microscopically the pericardium of Rabbit 254 showed only an extremely slight young connective tissue cell increase. In the latter, 255, there was marked congestion of the pericardium.

Rabbit 233, weight 1600 gm, was injected subcutaneously with 8 minims of Fowler's solution ten times, with seven or ten days between the injections, and was killed six weeks after the last injection. Microscopically at the juncture of the pericardium and the myocardium there was a slight infiltration with young connective tissue and lymphoid cells.

Rabbits 234, weight 2470 gm, and 237, weight 1950 gm, were injected subcutaneously with 10 minims of Fowler's solution for ten injections at seven- or ten-day intervals, extending over a period of three months. The former was killed six weeks and the latter eight weeks after the last injection. In both, microscopically, there were foci of young connective tissue and lymphoid cells at the juncture of the pericardium and the myocardium.

Rabbits 235, 236, and 238, weighing respectively 2520, 1920 and 1730 gm, were all given Fowler's solution by stomach-tube. Rabbit 235 received 10 minims in an equal amount of water, and Rabbits 236 and 238 got 8 minims with 10 minims of water. They all received ten doses at seven-day intervals and were killed nine weeks, six weeks, and eight weeks respectively after the last or tenth dose. Nothing abnormal was found macroscopically. Microscopically there were foci of young connective tissue and lymphoid cells at the juncture of the pericardium and the myocardium. Rabbit 238 showed a less marked picture and Rabbit 236 showed slight congestion also.

Rabbit 138, weight 2730 gm, was injected subcutaneously with 10 minims of Fowler's solution, and this was repeated two days later. For the next succeeding twenty days the rabbit was given a rest, because the urine showed that the rabbit had a severe acute nephritis. On the twenty-first day after the last or second subcutaneous injection, the rabbit was given 10 minims of Fowler's solution, plus 10 minims of water by stomach-tube, and this was repeated twice at three-day intervals. The stomach tube was used in this case rather than continuing subcutaneous injections, because there was a wide area of necrosis and sloughing of the abdominal wall. It might be stated here that in all the rabbits to which the arsenic was given subcutaneously there was marked necrosis followed by sloughing of the abdominal wall for quite an extensive area about the site of previous injection. This Rabbit 138 died three days after the last dose of Fowler's solution. Microscopically the pericardium was slightly infiltrated with young connective tissue cells and there were areas of marked congestion.

Rabbit 121, weight 2250 gm, was injected subcutaneously with 4 minims of Fowler's solution, this was repeated on the next day, and on the third day the dose was increased to 7 minims, which was repeated on the following day. On the fifth day the dose was increased to 10 minims and this was repeated every day for eleven injections. Thus the rabbit got sixteen injections in as many days. On account of marked sloughing and because the urine gave evidence of a nephritis, injections were suspended for four weeks. At the end of that time

the rabbit was given 10 minims of Fowler's solution by stomach-tube every day for five days. On the sixth day the rabbit died. Microscopically there was mild congestion of the pericardium and areas of hemorrhage at the juncture of the pericardium and the myocardium.

Rabbit 132, weight 2050 gm, was injected subcutaneously with 10 minims of Fowler's solution seven times in ten days, when the rabbit died. The pericardium showed no lesion either macroscopically or microscopically.

Rabbit 253, weight 2250 gm, was injected subcutaneously with ten minims of Fowler's solution at seven- and ten-day intervals for seven times and was killed eight weeks after the last injection. The pericardium was not abnormal.

Therefore, of the fourteen rabbits which were given arsenic in various ways over long and short periods, two showed no lesion of the pericardium, two others only congestion, four showed a very slight cellular increase, which was hardly more than normal, and six rabbits did have a slightly increased cellularity of the pericardium.

A fifth series of seven guinea-pigs of varying weights were injected subcutaneously at various intervals with varying doses of an aqueous solution of potassium bichromate.

Guinea-Pigs 136 and 137, weighing respectively 475 and 490 gm, were injected subcutaneously with 2 minims of a 5 per cent solution of potassium bichromate. The former, Guinea Pig 136, died four days and the latter died twelve days after the injection. Macroscopically the pericardium appeared normal. Microscopically, the pericardium of Guinea-Pig 136 showed areas of young connective tissue and lymphoid cells with congestion. In Guinea-Pig 137 there was a very slight young connective tissue and lymphoid cell infiltration both diffusely situated in the pericardium.

Guinea-Pig 179, weight 480 gm, was injected subcutaneously with 2 minims of a 1 per cent solution of potassium bichromate and this was repeated three, five, and nine days later. On the eleventh day the dose was increased to 4 minims of the 1 per cent solution, and on the thirteenth day again the dose was increased to 8 minims of the 1 per cent solution and the guinea-pig was injected as previously. This same dose was repeated five times at three week intervals and three times at weekly periods. Thus the guinea pig was injected subcutaneously fourteen times, four times with 2 minims, once with 4 minims, and nine times with 8 minims of a 1 per cent solution of potassium bichromate in four and one half months. The guinea-pig was killed ten days after the last injection. Microscopically the pericardium was a little thickened with an increase of young connective tissue and lymphoid cells with congestion and edema.

Guinea Pig 180, weight 465 gm, was injected exactly the same as No. 179 except that it survived only two injections of the 8 minim dose and died two weeks after the last or seventh injection, thus receiving mostly small doses. Microscopically the pericardium showed a similar picture to Guinea-Pig 179.

Guinea-Pig 187, weight 835 gm, was injected subcutaneously with 2 minims of a 5 per cent solution of potassium bichromate, and six days later with 5 minims of a 1 per cent solution. This was repeated in three days and again in two days later. After this the dose was increased to 8 minims and the guinea pig was thusly injected. Two days later the dose was again increased to 15 minims of a 1 per cent solution and the guinea-pig was injected and this injection was repeated six times at weekly intervals and twice more at three-week intervals. Eight weeks after the last or thirteenth injection the guinea-pig was killed. Microscopically at the base of the left auricle the pericardium was much thickened with young connective tissue and lymphoid cell infiltration, congestion, edema and increased vascularity.

Guinea-Pig 183, weight 400 gm, was injected subcutaneously with 5 minims of a 1 per cent solution of potassium bichromate. This was repeated in six days, again in two days, and two days later the dose was increased to 8 minims and the guinea-pig was injected. After this the injections were suspended for six weeks, and then the guinea-pig was again injected subcutaneously at weekly intervals with 8 minims of a 1 per cent solution for seven times. The guinea-pig was killed ten days after the last injection. Microscopically there was a slight increase of young connective tissue cells and slight congestion of the pericardium.

Guinea-Pig 184, weight 390 gm, was injected subcutaneously with 1 minim of a 1 per cent solution of potassium bichromate, and this was repeated every other day for six times, then the dose was increased to 8 minims of the 1 per cent solution, and the guinea-pig was thus injected two days later, and repeated in two weeks. The animal died the following day. Microscopically the pericardium showed considerable increase of young connective tissue and lymphoid cells.

Thus of the seven guinea-pigs which were injected subcutaneously with various amounts of potassium bichromate at various intervals, all showed some lesion of the pericardium, but in none was the lesion extensive or marked, usually only a slight increased cellularity being noted.

The last series consists of eighteen rabbits injected subcutaneously with potassium bichromate in doses of 21 minims of a 1 per cent solution at three-week intervals, this method seemed to give the best kidney lesion. A few rabbits, however, received smaller doses of a 5 per cent solution.

Rabbits 222, 223, 224, 225, and 231, weighing respectively 1300, 1530, 1730, 1700 and 1330 gm, were all injected subcutaneously on the same dates with 21 minims of a 1 per cent solution of potassium bichromate. Each rabbit was injected five times at three-week intervals and they were killed respectively ten, three, ten, nine, and eight weeks after the last injection. Microscopically nothing abnormal was noted. Microscopically Rabbits 222 and 225 both showed slight young connective tissue and lymphoid cell increase at the juncture of the pericardium and the myocardium. The pericardium of Rabbit 224 was very slightly infiltrated with young connective tissue cells with congestion. The pericardia of Rabbits 223 and 231 were not abnormal.

Rabbits 224, weight 2380 gm, 245, weight 2050 gm, 257, weight 2330 gm, and 258, weight 3310 gm, were all injected subcutaneously on the same dates with 21 minims of a 1 per cent solution of potassium bichromate. In all, each rabbit received four injections at three week intervals, and they were killed eight, eight, five and nine weeks respectively after the last injection. Macroscopically the pericardia were normal, and microscopically no lesion could be made out with the exception of Rabbit 244, whose pericardium showed a very slight young connective tissue cell infiltration with congestion.

Rabbits 262 and 263, weighing 1550 and 2000 gm, were injected with 21 minims of a 1 per cent solution of potassium bichromate two times with three weeks' interval between, and the rabbits were killed twelve weeks later. Macroscopically the pericardia of both were normal. Microscopically Rabbit 262 showed no lesion of the pericardium, but Rabbit 263 showed a slight young connective tissue and lymphoid cell infiltration at the juncture of the pericardium and the myocardium.

Rabbit 228, weight 1310 gm, was injected like the above for three times, and died three days after the last injection. Microscopically the pericardium was very slightly infiltrated with young connective tissue cells and slight congestion was present.

Rabbits 134, weight 1840 gm, and 135, weight 1880 gm, were injected subcutaneously with 0.5 cc of a 5 per cent solution of potassium bichromate. Ten days later Rabbit 134 was injected with 0.25 cc and Rabbit 135 was injected

with 0.5 c.c. of the same solution. After this 21 minims of a 1 per cent solution were injected subcutaneously at three-week intervals for four times. Both rabbits were killed eight weeks after the last injection. Their pericardia were not abnormal macroscopically. Microscopically there was a very slight diffuse increase of young connective tissue cells and also foci of these cells, both types of lesion being situated at the juncture of the pericardium and the myocardium.

Rabbits 131 and 133, each weighing 1900 gm., were injected subcutaneously with 1 c.c. of a 5 per cent solution of potassium bichromate. The former died five days and the latter six days after the injection. Microscopically Rabbit 131 showed a very slight young connective tissue and lymphoid cell infiltration at the juncture of the pericardium and myocardium. Rabbit 133, microscopically, showed proliferation of the pericardial cells, occasional foci of young connective tissue and lymphoid cells and areas of hemorrhage and edema at the juncture of the pericardium and the myocardium.

Rabbit 182, weight 2170 gm., was injected subcutaneously with 0.75 c.c. of a 5 per cent solution of potassium bichromate, and the rabbit died fourteen days later. Microscopically there were foci of young connective tissue and lymphoid cells at the juncture of the pericardium and the myocardium.

In this series of eighteen rabbits six showed no lesion of the pericardium, in six there was a slight increased cellularity, and in the remaining six rabbits the pericardium showed a fairly marked cellularity.

### *Summary*

Thus it is seen that the drugs used in these experiments, although in all cases there was a nephritis more or less marked, produced in no case a marked lesion of the pericardium, and in most animals there was only a slight deviation from the normal, and many showed no lesion at all, whereas, in the experiments with spartein sulphate and adrenalin chlorid, both injected intravenously, and in those where the spartein sulphate was used subcutaneously, followed by adrenalin intravenously, practically all rabbits showed a considerable and many showed a marked lesion of the pericardium.

Carney Hospital

## STUDY XV HEPATIC LESIONS ASSOCIATED WITH EXPERIMENTAL CARDIAC LESIONS

HENRY A. CHRISTIAN, M.D., BOSTON

In a study of experimental myocarditis produced by spartein sulphate and adrenalin chlorid carried on in this laboratory by Walker, fifty-seven rabbits received injections of these substances in varying dosage. The livers from these rabbits form the basis of this study.

The most striking thing in this series is the infrequency of hepatic lesions, in sharp contrast to the very constant cardiac lesions. Spartein and adrenalin appear to produce very slight direct change in the liver, at most as demonstrable in our animals, a transient congestion of the liver (active hyperemia) as shown in Figure 32\* from a rabbit (Rabbit

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\*All photographs for this series of articles were made by Mr. L. L. Brown, of the Massachusetts General Hospital for whose careful work I wish to express my thanks.

273<sup>35</sup>) dying shortly after receiving subcutaneously 0.025 gm spartein sulphate followed intravenously by 0.2 cc of a 1 to 1,000 solution of adienalin chlorid. On the other hand in some rabbits there result hepatic changes which are indirectly caused by the spartein and adienalin in the sense that these substances produce cardiac lesions and consequent to those passive congestion of the liver arises. Thus we have an experimental method of producing the hepatic lesions of chronic passive congestion in which the conditions are quite analogous to those found in man suffering from cardiac insufficiency. Unfortunately in only a few of these rabbits did the cardiac lesion advance to a stage of moderate decompensation, and only six showed hepatic changes interpretable as the consequence of passive congestion. However, these changes are in harmony with the views recently expressed by Mallory<sup>39</sup> in regard to the histogenesis of the hepatic lesions of chronic passive congestion, views contrary to those generally held by pathologists, and are described here mainly for that reason.

In five livers (Rabbits 266, 275, 280, 282, 283) the lesion present consists merely in a dilatation of the sinusoids, most marked in the vicinity of the central veins (terminal branches of the hepatic vein) and this dilatation is quite generally present throughout the liver. Figures 33 and 34 show this dilatation in contrast to the normal condition shown in Figure 35. Along with the dilatation of the sinusoids the liver cells show a moderate decrease in diameter. No other changes are found in these livers. The amount of dilatation varies in the several livers and in none is it extreme. This change appears to be a simple passive congestion of the liver consequent to the cardiac lesion.

In a fifth rabbit (Rabbit 79) of this series a very different hepatic lesion occurs. In the first place there is only moderate dilatation of the sinusoids, not very general in its distribution. This is notwithstanding the fact that a marked cardiac lesion existed and the heart functionally was decompensated as evidenced by a marked degree of edema and ascites. In the second place there is a very marked lesion distinctly irregular in its distribution consisting of the disappearance of liver cells and their replacement by blood corpuscles. This lesion corresponds in appearance with what is seen in the liver lobules of marked degrees of chronic passive congestion in man, a picture usually explained as arising from the atrophy and disappearance of liver cells and their replacement by dilated sinusoids. Figures 36, 37 and 38 show these lesions under moderate magnification and illustrate their focal character. More careful study of the changes in the liver of this rabbit shows that these lesions are irregularly distributed, being much more numerous in some sections than in others taken from different parts of the liver, however, as some

<sup>38</sup> For protocols of rabbits referred to, see end of this paper.

<sup>39</sup> Mallory. *Journal Med Research*, 1911, new series, *vi*, 455.



evidence of this change is found in all sections, the lesion is widely distributed. Their size varies from a small focus to an area occupying more than half the field of a Zeiss 16 mm objective with No 4 ocular. The lesion nearly always is closely adjacent to some branch of the hepatic vein, and very rarely extends peripherally so as to be in contact with branches of the portal vein. This distribution of lesion corresponds closely with that of extensive central necroses in human livers as described by Mallory<sup>40</sup> and is almost identical with the distribution of typical liver necroses of this type found in one rabbit (No 293) of this series in which there was no vascular or other lesion. In its most typical form the lesion consists of an area from whose center liver cells have entirely disappeared and there remain only red blood corpuscles, a small amount of hepatic reticulum and blood-vessel walls with connective tissue and endothelial cells. In the peripheral portion of such an area liver cells are found in different stages of degeneration. Many of these cells are more or less necrotic. The necrosis is evidenced by the cytoplasm staining pinkish to dark pink in contrast to the blue of the normal cytoplasm. The cytoplasm usually contains fine granules of yellowish pigment and the cells are smaller than the normal liver cell. The nuclei in some cells have disappeared, but as a rule the nuclei show much less change than does the cytoplasm. Almost always hemorrhage has taken place about the liver cells (Figure 39), and this is particularly well shown in sections stained by Mallory's anilin blue connective tissue stain where the blood corpuscles are plainly seen between the liver cell and the wall of the sinusoid (Figure 40). Polynuclear leukocytes to a slight extent wander into the space about the necrotic liver cells or penetrate them. At the periphery of many of these lesions transitions can be traced between slightly changed liver cells with a few red blood corpuscles about them to spaces from which liver cells have disappeared entirely, and their place has been taken by red blood corpuscles. In sections stained with the anilin blue connective tissue stain, foci where no liver cells appear can be seen to be made up very largely of red blood corpuscles filling spaces formerly occupied by hepatic cells, and in such areas the dilated sinusoid makes but a small part of the blood lake. In other places hemorrhage into pericellular spaces has taken place though the hepatic cells show very slight evidence of degeneration beyond atrophy and a changed granularity indicating some disturbance in the usual cytoplasmic architecture.

Scattered through the sections are groups of liver cells, almost always at the periphery of hemorrhagic foci such as are described above, which present a very different appearance from the cells showing necrosis. These cells have undergone a vacuolar change. They are very much swollen (Figure 41), their nuclei, centrally situated, stain quite well, in place of the usual granular cytoplasm there often remains only a few scattered

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<sup>40</sup> Mallory Jour Med Research, 1901, vi, 264

cytoplasmic granules and threads, some cells have a distinctly punched-out appearance as if all else than nucleus and cell membrane had disappeared, other cells have a distinct foam structure made up of medium-sized vacuoles. The exact relation of these liver cells to the hemorrhagic foci is not clear. The line of demarcation between hemorrhagic focus and vacuolated cells is usually sharp, but the two are ordinarily closely related. Sometimes sinusoids between the vacuolated cells are dilated, usually not. In a few places red blood corpuscles appear to have penetrated the cell membrane and are crowded about the nucleus. Possibly to a certain extent hemorrhagic foci form as a sequence of this type of cell degeneration. However, this cannot be said to be proved by the findings in this liver.

In addition to the changes already described only one other liver of the series showed a lesion, that was a fairly well-marked cirrhosis probably not associated with the spartein and adrenalin in a causative way, as it was quite similar to a type of cirrhosis occasionally met with in rabbits, either treated in various ways, or killed without any treatment for controls, and so presumably a spontaneous or accidental lesion.

### *Summary*

In a series of fifty-seven rabbits treated in various ways with spartein and adrenalin, very few hepatic lesions were found. In one focal necrosis and in another emphysematous changes were encountered, not believed to be associated with the drugs in a causative sense. In animals killed shortly after injections of larger doses of spartein and adrenalin acute hyperemia of the liver is found. In rabbits showing distinct cardiac lesions, two changes are found in the liver. One is a simple general dilatation of the central sinusoids with slight atrophy of liver cells, simple passive congestion, a mechanical effect. The other is a focal lesion with partial disappearance of liver cells and then replacement by blood. The latter change is the result of simple passive congestion combined with degeneration, mainly necrosis of liver cells as shown by the irregular distribution of the lesion and the presence of blood outside the sinusoids, either about degenerated liver cells or occupying the space remaining after the total disappearance of the liver cells, simple passive congestion plus focal liver degeneration, a mechanical effect in combination with a toxin of some kind producing cell injury and interstitial hemorrhage.

### PROTOCOLS OF RABBITS REFERRED TO IN THE PAPER

PROTOCOL 79—Rabbit Weight 1700 gm December 12, 1908, spartein sulphate 0.021 gm, adrenalin chlorid 0.2 cc, both subcutaneously. January 25, same February 19, spartein sulphate 0.021 gm, adrenalin chlorid 0.26 cc, March 16, same April 9, weight 2100 gm. Spartein sulphate 0.025 gm subcutaneously, adrenalin chlorid 0.2 cc intravenously. Killed April 24, 1909. Weight 2280 gm.

*Autopsy*—There is definite, well-marked edema of the subcutaneous tissue and the scrotum. The peritoneum contains 115 cc of fluid with a specific gravity of 1.018. Liver, weight 102 gm, appears very large. Its surface is mottled in

color, being dark red, checkered over with a tracery of lighter grayish red areas corresponding apparently to lobules and giving the appearance of a nutmeg liver. Pleural cavities are filled with fluid. Heart, right ventricle is of normal consistence, as is the right auricle. The left auricle is distinctly thickened, feels firmer than right. The left ventricle from a point a little below the auriculo-ventricular groove almost down to the apex feels dense, the wall is thickened and is paler in color than other parts of the heart. Lungs, reddish pink, exuding a considerable amount of frothy serum from the cut surface.

PROTOCOL 266—Rabbit December 7, 1909, spartein sulphate 0.025 gm intravenously, adrenalin chlorid 0.2 cc intravenously. December 9, spartein sulphate 0.025 gm, adrenalin chlorid 0.2 cc, both intravenously. December 13, 16, 20, January 5, same. January 10, spartein sulphate 0.018 gm, adrenalin chlorid 0.2 cc, both intravenously. January 13, spartein sulphate 0.0125 gm, adrenalin chlorid 0.2 cc, both intravenously. Died January 13. Weight 1420 gm.

*Autopsy*—No free fluid in the cavities except small amount of muddy fluid in the pericardium. Quite firm fibrous adhesions between the two layers of the pericardium. Heart appears large, weight, 6.05 gm, surface rough from torn adhesions. Kidneys, weight, 9.55 gm, on section show a narrow whitish cortex with prominent glomeruli, while the medulla is of a dark brownish color.

PROTOCOL 273—Rabbit December 24, 1909, spartein sulphate 0.025 gm subcutaneously, adrenalin chlorid 0.2 cc intravenously. Died December 24. Weight 2170 gm.

*Autopsy*—No free fluid in the cavities of organs injected. Heart, weight, 7.5 gm. Kidneys, weight 13.3 gm.

PROTOCOL 275—Rabbit December 24, 1909, spartein sulphate 0.025 gm subcutaneously, adrenalin chlorid 0.2 cc intravenously. Died in 15 minutes.

*Autopsy*—Much free fluid in the abdominal cavity. Heart, weight, 8.1 gm. Kidneys, weight, 13.3 gm.

PROTOCOL 280—Rabbit January 5, 1910, spartein sulphate 0.03 gm, adrenalin chlorid 0.2 cc, both intravenously. January 10, spartein sulphate 0.018 gm intravenously. Animal died almost immediately.

*Autopsy*—Much free blood stained fluid in the abdominal, pleural and pericardial cavities. Heart, weight, 7.5 gm. Kidneys, weight, 10.65 gm.

PROTOCOL 282—Rabbit January 31, 1910, spartein sulphate 0.007 gm, adrenalin chlorid 0.1 cc, both intravenously. Repeated Feb 2, 4, 9, 11, 14, 17, 24. February 28, spartein sulphate 0.008 gm, adrenalin chlorid 0.1 cc, both intravenously. February 28, spartein sulphate 0.008 gm, adrenalin chlorid 0.1 cc. March 2, spartein sulphate 0.008 gm, adrenalin chlorid 0.1 cc. March 5, spartein sulphate 0.008 gm, adrenalin chlorid 0.1 cc. March 7, spartein sulphate 0.008 gm, adrenalin chlorid 0.1 cc. March 9, spartein sulphate 0.008 gm, adrenalin chlorid 0.1 cc. March 12, spartein sulphate 0.008 gm, adrenalin chlorid 0.1 cc. Same on March 14, all injections intravenously. Died on March 14.

*Autopsy*—Slight amount of bloody fluid in abdominal, pleural and pericardial cavities. Heart, weight, 10.1 gm, appears large, left ventricle and auricle very firm and thickened, with a large whitish area near the auriculoventricular groove in the left ventricle. Kidneys, weight 19.1 gm.

PROTOCOL 283—Rabbit Spartein sulphate 0.007 gm, adrenalin chlorid 0.1 cc. Repeated February 2, 4, 9, 11, 14, 17, 24, 28. March 2, spartein sulphate 0.008 gm, adrenalin chlorid 0.1 cc. Repeated March 5, 7, 9, 12, 14, 16, 19, 21, 23, March 28, spartein sulphate 0.02 gm, adrenalin chlorid 0.1 cc. Repeated March 31. April 2, spartein sulphate 0.025 gm, adrenalin chlorid 0.165 cc. Repeated April 4, 6, 9, all injections intravenously. Died April 9.

*Autopsy*—Right pleural cavity filled with pus. Upper half of right lung solidified. Pericardium much thickened with adhesions. Heart is enlarged.

PROTOCOL 293—Rabbit March 30, spartein sulphate 0.04 gm, adrenalin chlorid 0.2 cc, both intravenously. Killed March 31.

*Autopsy*—Slight amount of straw colored fluid in the abdominal cavity, considerable amount in pleural cavity. Pericardial cavity filled with bloody fluid.

# A MODIFICATION OF WOHLGEMUTH'S METHOD FOR THE QUANTITATIVE STUDY OF THE ACTIVITY OF THE PANCREATIC FUNCTION ~

P B HAWK, PH D  
URBANA, ILL

The method suggested by Wohlgemuth<sup>1</sup> for the quantitative determination of fecal amylase does not yield dependable data when stools of a pronounced acid reaction are under examination. The principle of Wohlgemuth's method is the extraction of a weighed portion of feces with 1 per cent sodium chlorid solution and the determination of the amylolytic activity of gradually decreasing volumes of this centrifugated extract, by means of a series of tubes in each of which 5 cc of 1 per cent soluble starch is used as substrate. After twenty-four hours at 38 C these tubes are treated with a solution of iodine and the extent of digestion determined colorimetrically.

In case the stools do not vary in reaction to any pronounced degree from the normal limits, the above procedure of Wohlgemuth is satisfactory for ordinary clinical purposes. However, when the dietary or metabolic régime of the patient is such as to cause the production of stools which are strongly acid in reaction, the sodium chlorid extracts of such stools will possess such a high acid concentration as to render the interpretation of the findings obtained by means of this method, rather open to question. In a recent investigation as to the influence of water-drinking at meal-time on the activity of the pancreatic function<sup>2</sup> I used Wohlgemuth's method. Certain stools were encountered during the period in which large volumes of water were being daily ingested, which gave evidence of an amylolytic activity several times greater than that possessed by the other stools examined. In searching for an explanation as to this increased starch-hydrolyzing property, I found the stools in question to possess a very strong acid reaction. The question then arose as to the interpretation of the amylolytic power of the feces. Was this increased amylolysis to be interpreted as a sure indication of a stimulated pancreas, or was there a possibility that the acid reaction of the stools had introduced an uncontrolled factor, which vitiated, to a degree, the findings obtained by means of the method in question?

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\* From the Laboratory of Physiological Chemistry of the University of Illinois

1 Wohlgemuth *Berl klin Wehnschr*, 1910, xlvii, 92

2 Hawk *THE ARCHIVES INT MED*, 1911, viii, 382

It has been demonstrated that amylase is very susceptible to the influence of acids. For example, Chittenden and Griswold<sup>3</sup> have shown that the presence of a trace of acid will facilitate the action of the enzyme, whereas an acidity but slightly in excess of that bringing about optimum activity of the enzyme will cause absolute inhibition. These findings were verified by Vernon,<sup>4</sup> who also demonstrated the inhibitory influence of alkali. Vernon determined that the enzyme was four times as active in the presence of 0.004 per cent hydrochloric acid as in a neutral solution and moreover, that an acid concentration of 0.009 per cent hydrochloric acid entirely inhibited the action of the enzyme. Further tests with organic acids such, for example, as lactic acid and acetic acid, yielded similar findings, it being shown, in general, that traces of organic acids facilitated the action of the enzyme, whereas acid concentrations but slightly in excess of these, caused complete inhibition. The amylase possessed the optimum activity in the presence of 0.0083 per cent lactic acid. A similar stimulation of amylase activity, through the proper acid concentration, has been demonstrated by Schierbeck,<sup>5</sup> who also determined the retarding action of alkali.

Bearing in mind the facts just cited regarding the influence of acid on the action of amylase, it seemed entirely possible, therefore, in the case of the stools in question in this investigation, that the hydrogen ion concentration of the feces as passed was sufficient to impart to the sodium chlorid extracts, as prepared in the Wohlgemuth technic, the proper hydrogen ion concentration to induce the optimum activity of the amylase. The hydrogen ion concentration of the sodium chlorid extracts of the other stools examined was evidently not sufficient to cause any appreciable augmentation of the enzyme activity above that possessed by the amylase in neutral solution. It is evident, therefore, that only neutralized extracts should be examined, if the application of Wohlgemuth's method is to be of any real service to the clinician and in order to eliminate the question of uncertainty in connection with the interpretation of the data obtained from stools possessing a concentration of H or OH ions, far above the normal limits.

If we attempt to use indicators to determine the neutrality of the fecal extracts, we are at the outset confronted by a serious difficulty. Under all conditions the extracts possess a brownish cast of color, the depth of which depends on the quantity of pigment present. After a series of testings we can, of course, bring the extract to the neutral point, but our testings have been instrumental in removing a certain amount of the fecal extract which has been carried into the indicator paper by capillary attraction. This method of neutralization also causes the fecal

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<sup>3</sup> Chittenden and Griswold. *Am. Chem. Jour.*, 1881, **111**, 305.

<sup>4</sup> Vernon. *Jour. Physiol.*, 1901-02, **xxvii**, 174.

<sup>5</sup> Schierbeck. *Skandin. Arch. f. Physiol.*, 1892, **111**, 344.

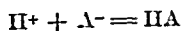
extracts from day to day to assume a variable electrolyte content. This fact of itself would introduce an error, inasmuch as Sherman<sup>6</sup> and collaborators have recently shown that pancreatic amylase is greatly influenced by the electrolyte concentration. Still more recent evidence in this connection has been furnished by Lisbonne<sup>7</sup> and by Gerber.<sup>8</sup> A neutral solution could, of course, be obtained by dialysis, but this manipulation would entail considerable extra labor, and the amylase value of the stools under examination would not be available inside of forty-eight hours from the time they were passed.

The problem was finally solved by the use of a phosphate mixture<sup>9</sup> as the extraction medium.<sup>10</sup> This phosphate mixture contains 0.1 mol dihydrogen sodium phosphate and 0.2 mol disodium hydrogen phosphate per liter. This was prepared in a 1 per cent solution of sodium chloride, in order to produce a sufficiently high electrolyte content to insure satisfactory amylolytic action. By the use of this phosphate mixture as an extraction medium, we secure a neutral extract, even though the feces should possess a rather higher H or OH ion concentration than is normally met with.

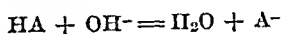
The action of such a solution, in maintaining a constant hydrogen and hydroxyl ion concentration, is explained by the aid of the ionic theory as follows. Under the conditions outlined above, we have a solution of the two phosphates such that the equilibrium constant

$$K = \frac{(\text{H}^+) (\text{A})}{(\text{HA})}$$

is approximately equal to  $1 \times 10^{-7}$  or to the concentration of the hydrogen ion in pure water, i. e., the solution is neutral. If we add an acid to this solution, then the excess of hydrogen ion derived from the acid will be removed according to the reaction



and likewise, if we add an alkali the excess of hydroxyl ion will be removed according to the reaction



That is, a mixture of a weak acid and a salt of this acid in the proper proportions will tend to preserve itself in a neutral condition, within certain limits, when treated with varying amounts of acid or alkali. The

6 Sherman, Kendall and Clark *Jour. Am. Chem. Soc.*, 1910, **XXXII**, 1073.  
 Sherman and Kendall *Jour. Am. Chem. Soc.*, 1910, **XXXII**, 1087.

7 Lisbonne *Compt. rend. Soc. de biol.*, 1911, **LXX**, 132.

8 Gerber *Compt. rend. Soc. de biol.*, 1911, **LXX**, 391.

9 Washburn *Jour. Am. Chem. Soc.*, 1908, **XXX**, 31, Henderson and Webster  
*Jour. Med. Research*, 1907, New Series, **VI**, 1, Henderson *Am. Jour. Physiol.*,  
 1906, **IV**, 257, 1908, **XXI**, 173.

10 I am indebted to Professor E. W. Washburn of the University of Illinois for suggesting the use of this phosphate mixture for this purpose.

mixture of  $\text{Na}_2\text{HPO}_4$  and  $\text{NaH}_2\text{PO}_4$  in the proportion 2 to 1, as mentioned above, satisfies the condition as outlined for the preservation of a neutral solution

If the method described in this paper is followed, the electrolyte concentration of the various fecal extracts will also be very uniform, the only variation being due to any slight variation which may be possessed by the different stools under examination. When it is recalled that only 2 gm of moist feces are employed, and further that this amount of feces is extracted with a 1 per cent solution of sodium chlorid containing phosphate as already indicated, it is evident that the variation in the electrolyte concentration of different fecal extracts is entirely negligible.

In harmony with the above facts I would suggest the following modification of Wohlgemuth's method

Weigh accurately about 2 gm of fresh feces into a mortar,<sup>11</sup> add 8 cc of a phosphate-chlorid solution (0.1 mol dihydrogen sodium phosphate and 0.2 mol disodium hydrogen phosphate per liter of 1 per cent sodium chlorid), 2 cc at a time, rubbing the feces mixture to a homogeneous consistency after each addition of the extraction medium. Permit the mixture to stand at room temperature for a half-hour with frequent stirring. We now have a neutral fecal suspension. Transfer this suspension to a 15 cc graduated centrifuge tube being sure to wash the mortar and pestle carefully with the phosphate-chlorid solution and add all washings to the suspension in the centrifuge tube. The suspension is now made up to the 15 cc mark with the phosphate chlorid solution and centrifugated for a fifteen-minute period, or longer if necessary, to secure satisfactory sedimentation. At this point, read and record the height of the sediment column. Remove the supernatant liquid by means of a bent pipette, transfer it to a 50 cc volumetric flask and dilute it to the 50 cc mark with the phosphate-chlorid solution. Mix the fecal extract thoroughly by shaking and determine its amylolytic activity. For this purpose a series of six graduated tubes is prepared, containing volumes of the extract ranging from 2.5 cc to 0.078 cc. Each of the intermediate tubes in this series will thus contain one-half as much fluid as the preceding tube. Now make the contents of each tube 2.5 cc by means of the phosphate chlorid solution in order to secure a uniform electrolyte concentration. Introduce 5 cc of a 1 per cent soluble starch solution<sup>12</sup> and three drops of toluol into each tube, thoroughly mix the contents by shaking, close the tubes by means of stoppers and place them in an incubator at 38 C for twenty-four hours. At the end of this time remove the tubes, fill each to within half an inch of the top with ice water, add one drop of tenth-normal iodine solution, thoroughly mix the contents and examine the tubes carefully with the aid of a strong light. Select the last tube in the series which shows entire absence of blue color, thus indicating that the starch has been completely transformed into dextrin and sugar, and calculate the amylolytic activity on the basis of this dilution. In case of indecision between two tubes, add an extra drop of the iodine solution and observe them again.<sup>13</sup>

11 Duplicate determinations should be made

12 In preparing the 1 per cent solution, the weighed starch powder should be dissolved in cold distilled water in a casserole and stirred until a homogeneous suspension is obtained. The mixture should then be heated with constant stirring, until it is clear. This ordinarily takes from eight to ten minutes. A slightly opaque solution is thus obtained, which should be cooled and made up to the proper volume before using.

13 Theoretically we would expect the colors to range from a light yellow to a dark blue, with red tubes holding an intermediate position in the series. This color sequence does often occur, but its occurrence is far from universal. Many

## CEREBROSPINAL MENINGITIS DUE TO BACILLUS INFLUENZÆ

A REPORT OF TWO CASES, FROM ONE OF WHICH THIS ORGANISM WAS OBTAINED IN PURE CULTURE FROM THE CIRCULATING BLOOD EIGHTY-FIVE DAYS BEFORE DEATH \*

LAWRENCE J RHEA, M D  
MONTREAL, CANADA

Nervous phenomena in influenza are very common, but if we are to judge from the cases reported in the literature, meningitis due to *Bacillus influenzae* alone is uncommon

Cohoe<sup>1</sup> in 1909 reviewed the cases that had been reported up to that time and added one case of his own. He was able to collect reports of twenty-four cases in which the diagnosis was based on bacteriological findings. Fifty-six per cent of these cases occurred in children under 1 year of age. Eighty-five per cent of the patients in Cohoe's review died, most of the cases came to autopsy. During the past two years several new cases have been reported.<sup>2</sup>

The gross changes in the central nervous system of patients dying from influenzal meningitis have shown great variation in their situation, extent and character. In most cases the lesions are confined to the tissues of the meninges but the gray and white matter of the brain and cord may be involved. The meningeal involvement is generally confined to the cerebrum, and the extent of the lesions in this location varies greatly. In some cases only very small areas, in others the greater part of the cerebral meninges, are affected. The gross character of the lesion in the meninges is not constant. In some of the cases no gross pathological changes could be seen, in others there was only congestion of the blood-vessels, but there may be frank exudate, indistinguishable from that produced by the pneumococcus or meningococcus, intrapial ecchymoses, or large or small intrapial hemorrhages. The macroscopical changes in the gray and white matter of the brain and spinal cord vary with the

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\*Read before the American Association of Bacteriologists and Pathologists, May, 1910

1 Influenza Meningitis. Am Jour Med Sc, 1909, cxxxvii, 74

2 Davis, Tr Chicago Path Soc, 1910, viii, 39-44, reports seven cases of influenza meningitis. From two of these cases *Bacillus influenzae* was obtained in pure culture. Meyer in an article entitled Ueber akute genuine Encephalitis, Frankf Ztschr f Path, 1910, v, 532, gives reference to several articles on influenza infections of the central nervous system.



## CONGENITAL OBLITERATION OF THE BILE-DUCTS

C P HOWARD, M D, AND S B WOLBACH, M D

IOWA CITY, IA

BOSTON

Congenital obliteration of the bile-ducts, though long recognized and reported with relative frequency in medical literature, is still, we believe, sufficiently rare condition to warrant an additional clinical and pathological report. The history and pathological findings of a case will first be given, and subsequently the incidence, symptomatology, gross and microscopic anatomy and pathogenesis will be discussed.

### I REPORT OF CASE

*Patient*—J M, age 6 weeks, male, Hebrew, was admitted on March 24, 1910, to the children's clinic and subsequently to the service of Dr Finley of the Montreal General Hospital. The complaint was "yellowness of the skin." The following history was obtained from the mother.

*Family History*—The father was living and well at 42 years, the mother was living and well at 35. When 18 years of age, during her first year of marriage, she had a miscarriage at the fourth month. One year later a child was born at full term but died three weeks after birth. A third pregnancy did not occur until seven years later, and the fourth and fifth followed in rapid succession. All of the three latter resulted in full-term, healthy children who are at present 10, 8 and 5 years old, respectively. As far as she remembered, none of them was jaundiced at birth or during infancy.

*Personal History*—Thus, the sixth pregnancy was uneventful, the mother was running perfectly well during the entire period. The birth occurred at full term and was normal. The child was fat, healthy-looking and not noticeably jaundiced at birth. It was breast-fed for the first seven days when it was weaned on account of a maternal puerperal infection which necessitated the mother being removed to a hospital on Feb 16, 1910. There a clinical diagnosis of puerperal infection and pelvic cellulitis was made. When last seen by the mother she stated that the child was healthy and not noticeably jaundiced. During her absence the child was sent by the Baron de Hirsch Institute to the Montreal Foundling Hospital.

*Present Illness*—Through the kindness of Dr J L D Mason of the Baron de Hirsch Institute and Drs Wyld and Hill of the Foundling Hospital we subsequently learned that on February 23, the day of admission to the latter institution, and when the baby was two weeks of age, a slight but definite jaundice of the skin and light colored stools were present, further, that on March 2, after a course of calomel, the jaundice became very deep and the stools clay-colored. The child steadily lost in weight, falling from 7 4 pounds to 6 1 pounds.

\*From the Clinic and Laboratory of the Montreal General Hospital, read before the American Association of Pathologists and Bacteriologists at the seventh Annual Meeting, Chicago, Ill, April 14, 15, 1911.

on March 2, the date of its discharge. On March 8 the mother first saw it again and noted the deep jaundiced hue to the skin and scleræ. About March 14, when the baby was five weeks old, the mother first noticed that the urine was very dark in color, and that it stained the diapers and everything with which it came in contact a deep yellow. The bowels became loose with from four to five colorless and offensive stools in the twenty-four hours. At the same time vomiting developed. From March 2 to the date of admission to the hospital, the child had been fed on cow's milk diluted with equal parts of water. It was brought to the children's clinic on March 24 when a diagnosis of icterus neonatorum, due probably to syphilitic hepatitis, was made. It was sent into the hospital in the service of Dr. Finley, to whose courtesy we are indebted for subsequent observation and study of the case.

*Physical Examination*—The patient was a very poorly nourished, male Hebrew child six weeks of age. The weight on admission was 7 pounds, 6 ounces (3,300 grams). The expression was anxious and the child was fretful to a degree. There were no snuffles or other luetic stigmata. The skin was deeply jaundiced and of a distinct coppery hue that offended the eye. Scattered over the skin of the thorax was a fine miliary rash. The scleræ were deeply jaundiced. The muscles were small, the bones normal. The anterior fontanelle was still widely patent. The lymph-glands were nowhere palpable.

*Respiratory System* There was frequent cough but no dyspnea. The thorax was small and of the normal infantile type. No heaving of the ribs was found. The percussion note was resonant throughout. The breath sounds were puerile, but the presence of adventitious sounds was impossible to determine owing to the constant crying of the child on examination. The heart was not enlarged and the sounds were clear. The pulse was rapid, small, regular and of normal tension.

The abdomen was full and rounded. The superficial veins were everywhere prominent, especially while the child cried, and there was a slight but definite anastomosis visible between the lower thoracic and superficial epigastric veins on either side.

The liver was considerably enlarged but the surface appeared smooth and the edge thin and firm. The upper border of the relative hepatic dulness began at the fourth rib in the right parasternal line, the fifth rib in the mid axillary line, and extended below the costal border 5 cm and 3.5 cm respectively, making a total vertical dulness of 9.5 cm.

The edge of the spleen could just be felt at the costal border.

The urine was deeply bilious, almost porter colored, and gave the well-marked characteristic rings with fuming nitric acid. The stools were very offensive, perfectly colorless and in this and in their peculiar consistency, resembled white lead.

*Course of Disease*—On March 26, 1910, a blood count revealed hemoglobin 50 per cent (Sahli), red cells 3,910,000, white cells 15,800. The smears stained by Wright's method showed normal red cells with a preponderance of polymorphonuclear neutrophils and no pathological cells. A Wassermann reaction on this date was reported absent by Dr. R. P. Campbell. Nevertheless, the therapeutic test of a course of mercurialunctions was given without benefit.

For the first ten days the temperature ranged between 98 and 99.4, the pulse between 112 and 136 and the respiration 48 to 60 per minute. From April 1 to the day of the child's death, on April 18, the temperature curve was most irregular, ranging between 97 and 101. The pulse grew more frequent, namely, 120 to 138 per minute, while the respiration fell to 40 or less per minute. The child cried constantly day and night but took its nourishment, consisting of modified milk, fairly well.

On April 9 it was noted that even with careful regulation of the diet, the child was steadily failing. The lungs were apparently clear, though there was a frequent hacking cough present. The jaundice persisted and did not vary

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noticeably in intensity in spite of frequent doses of calomel. The diarrhoea abated, the weight fell steadily to 6 pounds, 9 ounces (2,986 grams) on April 14. On the afternoon of April 18, death occurred suddenly, after the child had been under observation for twenty-six days and during the tenth week of life.

An autopsy was performed by Drs Wolbach and Baird on April 22, 1910, four days after death, owing to the difficulty of communicating with the mother. The body, which was 51 cm in length, was very poorly developed and poorly nourished, with marked general jaundice and lividity of the dependent parts. Except for the disappearance of rigor mortis there was otherwise no evidence of post-mortem decomposition.

The right pleural cavity showed fresh adhesions between the diaphragm and the right lower lobe, on separating which a thick, gelatinous, greenish-yellow, fibrous material was found, small in amount. The left cavity was quite free. The lungs were both voluminous and air containing, except the lower right lobe, which presented over its base and posterior surface a nodular appearance, due to small, yellow, rounded, soft elevations 4 to 6 mm in diameter. On section of this lobe, its anterior half was found riddled with a series of cavities, small, rounded and separated only by thin, smooth walls and containing a thick, gelatinous, greenish-yellow puriform material. A careful dissection of the bronchi showed these cavities to be dilatations of their walls.

The pericardium was smooth and glistening. The heart weighed 20 gm and appeared slightly enlarged. The endocardium and valves were normal. The myocardium was smooth, firm and of good color.

The peritoneal cavity was smooth and glistening and both parietal and visceral surfaces were stained a deep yellow. The mesenteric lymph-nodes were slightly enlarged, dark and soft, and yellow in color on section.

The liver was enlarged, its lower border reaching 3 cm below the costal margin. After preservation in Kaiserling, it weighed 370 grams and measured 12.5 cm transversely, 8.5 cm anteroposteriorly, and 5 cm vertically. The weight and measurements were no doubt somewhat greater before preservation but unfortunately were not recorded. The surface was smooth except for an occasional slight depression. The color was a very dark brownish-green. The shape, relative size of the lobes and the position of the fissures were normal. The anterior edge was sharp, the consistency firm and slightly tougher than normal. On section the cut surfaces were smooth, dark and mottled, due to minute greenish black areas separated by a delicate dark red tracery.

The gall-bladder was very small and presented as a bulbous enlargement of the cystic duct 1 cm long and 0.5 cm broad. It could be filled with water from a hypodermic syringe, but no fluid escaped from the cystic duct. The anatomical relations of the gall-bladder, hepatic, cystic and common ducts and the vessels of the liver were normal. The hepatic, cystic and common ducts consisted of fibrous cords in which no lumen could be found either by a probe or by injection with a hypodermic syringe.

On opening the duodenum, the papilla of Vater was easily found. No fluid could be forced through it by milking the bile passages. A probe passed into the papilla entered without resistance into the pancreatic duct. A very careful dissection with a probe in the pancreatic duct failed to show any other structure entering the duodenum in the neighborhood of the papilla. A similarly cautious dissection downward along the cord representing the common duct carried one into the head of the pancreas, where the common duct lost itself in the substance of the pancreas as a number of delicate fibrous strands (Fig 5).

The spleen weighed 25 gm (15 gm is the average weight of the spleen in the third month), was smooth, dark red in color and of normal consistency. On section the surface was dark red and yielded no pulp on scraping. The pancreas was normal in appearance and consistency. A careful dissection as stated above, showed that its duct opened normally into the duodenum. The gastro-intestinal tract was normal throughout.

The kidneys weighed 45 gm, both were smooth, dark red in color and of normal contour. The capsules peeled off easily. On section the cortices and pyramids were normal. The adrenal glands and genital organs were normal. The bone marrow appeared normal.

The brain weighed 440 gm and presented no apparent lesion. The anatomical diagnosis was congenital obliteration of the bile passages, rudimentary gall-bladder, bronchiectasis (local), hydropneumothorax and pleurisy and icterus.

*Microscopic Examination*—Sections were stained with Scharrlach red, hematoxylin methods.

The heart was quite negative.

A section from the normal-appearing portion of the lung showed moderate injection of the alveolar capillaries. The vessels and bronchi were negative. Occasional groups of alveoli contained a few polymorphonuclear leukocytes and desquamated epithelium. Sections from the right lower lobe were riddled with cavities, mostly circular in outline, and containing puriform material and separated from one another by narrow zones of flattened alveoli filled with exudate. In many of these cavities portions of the periphery were bounded by cuboidal epithelium. Some of the small cavities were completely surrounded by cuboidal cells, a few of which showed ciliated borders. In most instances the border of these cavities was sharply demarcated and occasionally showed a definite line suggesting the basement membrane of the bronchus. By the use of Mallory's connective-tissue stain, smooth muscle fibers were occasionally found external to the line bounding the cavity, which was further evidence that these cavities were bronchiectatic in origin. The contents of the cavities were composed chiefly of polymorphonuclear leukocytes and cell debris. There were numerous phagocytic cells containing nuclear remains and, rarely, red-blood corpuscles. Where the boundaries were poorly defined and the adjacent alveoli merged in the puriform areas, there were occasional compact masses of eosin stained material filled with migrating leukocytes and nuclear fragments, remotely suggestive of caseous material. Stains for tubercle bacilli, however, yielded negative results. The alveoli between the puriform areas were compressed and many contained pus, a few fibrin and a few large, sponge like, mononuclear cells. All of the bronchi in these sections were filled with puriform material. The blood-vessels were negative. The interlobular connective tissues were edematous.

The liver was moderately injected. The normal area of the liver columns was preserved, but there was a distinct loss of cells and increase in the connective tissue about the hepatic veins and a fairly marked increase about the portal spaces. The liver cells themselves stained normally. At the centers of the anatomical lobules, the bile capillaries were filled with dark brown inspissated bile and were often greatly distended or ruptured. There were masses of bile lying outside the liver columns, some of which were taken up by endothelial cells. In most lobules there was a considerable increase of connective tissue in the spaces formerly occupied by liver cells and now containing pigment and phagocytic cells. The cells of the intermediate zone were normal, except for a small amount of pale, brown, granular pigment scattered throughout the cytoplasm. At the periphery of the lobules there was often an irregular increase of the connective tissue extending inward from the portal space between the liver columns and sinusoids. Many of the portal spaces contained a large number of tortuous bile ducts, empty of bile. The bile capillaries at the periphery of the lobules were easily demonstrable, but were also empty. Most of the large bile ducts in the portal spaces showed no evidence of dilatation and contained a circular reticulum only, rarely a dilated bile duct was found filled with inspissated bile and lined with flattened epithelium. No fat could be demonstrated.

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The spleen showed moderate injection. The Malpighian bodies were normal. The pulp contained a few large mononuclear cells, phagocytic for red-blood corpuscles.

The kidneys were markedly injected. The glomeruli were of the normal fetal type. The epithelium of the convoluted tubules was swollen and granular. There was an occasional hyaline cast in the collecting tubules. The adrenals and other organs were normal.

The histological diagnosis was bronchiectasis of the lower lobe of the right lung, hepatic cirrhosis of a mixed type, subacute nephritis.

## II ETIOLOGY AND SYMPTOMATOLOGY

*Historical Note*—For many years icterus neonatorum was recognized before it was realized that a certain small percentage of these cases was associated with malformations of the biliary tract. From time to time isolated examples have been reported of icterus developing at birth or shortly afterward, which was found post mortem to be associated with stenosis or even complete obliteration of the hepatic, cystic or common ducts. John Thomson,<sup>1</sup> in 1892, was the first writer to assemble the various cases in the literature. He was able to collect forty-nine protocols and wrote a classical article which has formed the basis for most of the subsequent reviews. In 1901, H. D. Rolleston and L. B. Hayne<sup>2</sup> added nine cases to Thomson's series, bringing the total to fifty-nine. The last important article was published in 1908 by Lavenson,<sup>3</sup> who abstracted sixty-two acceptable cases and added a case of his own.

We have succeeded in finding thirteen additional cases, which either have been overlooked by Lavenson (e. g., Kumisson and Hebert,<sup>4</sup> Cattaneo,<sup>5</sup> Demel,<sup>6</sup> Bushnell,<sup>7</sup> Emanuel,<sup>8</sup> Simmonds,<sup>9</sup> [two cases], Miller<sup>10</sup>) or have appeared since his paper (Parkes Weber,<sup>11</sup> Peck,<sup>12</sup> Petit and Meile,<sup>13</sup> M. and R. C. Ferrard<sup>14</sup>).

This now brings the total number of cases of congenital obliteration of the bile-ducts to seventy-six, inclusive of ours and exclusive of those directly associated with syphilis (Rolleston,<sup>15</sup> Simonini<sup>16</sup>).

*Predisposing Factors*—1. *Health of Parents*. Some minor rôle may be played by the health of the parents prior or subsequent to conception. Thomson found that of ninety-six parents, five had had at one time or another, syphilis. In others, again, there was a history of recent severe digestive derangement (e. g., Ferrard<sup>14</sup>). In our case, while no definite history of lues could be elicited, it is noteworthy that during the early married life of the mother, there was a miscarriage at the fourth month that the second child, though born at full term, died three weeks after birth, and that the third pregnancy did not occur until seven years later.

2. *Condition of Other Children in the Family*. Several authors have noted a tendency for more than one child of the same parents to have icterus, two authors reporting two cases in the same family in association with a defect of the bile-passages. Again, another author reported twins, both of whom were jaundiced but one recovered so that the condition of its bile-passages was not ascertained.

3. The Character of Labor This has been for the most part entirely normal, at least no history of excessive trauma has been noted in any of the series With Thomson, we admit that trauma or exposure at the time of birth might cause a local peritonitis and so, obliteration of the ducts

4 Premature Birth This plays no rôle, for, though it was found five times in Thomson's series, in all of the five jaundice did not develop until some time subsequently

5 Sex Curiously enough, male infants seem more predisposed than female, but in so small a series too much emphasis should not be laid on this factor

6 Congenital Syphilis Six, possibly nine of Thomson's series presented evidence of congenital lues at birth or shortly afterward In our case there were no apparent stigmata and the Wassermann reaction proved negative Hence, it is safe to say that in the majority of cases there is no sign or suspicion of lues

7 Erysipelas This, which has been suggested by one or two writers as a possible predisposing factor, can be dismissed without further comment

*Symptomatology*—1 Onset of Jaundice The period of the onset of jaundice varies considerably In some cases the icterus is noticed on the day of birth, in others not until the child is 2 weeks or more old Naturally, there are many possible sources of error for such discrepancies as, for example, the jaundice may be very faint at birth and will only be noted when it becomes of a certain intensity With Rolleston we cannot accept Treves' remarkable case in which the onset of the jaundice did not occur until the third year of life and in which a successful operation for the relief of the obstruction was performed at the age of 17 As Rolleston suggests, the obstruction was in all probability due to calculus or some postnatal infection of the duct At least one must admit that some event at birth plays a part in determining the onset of the color Legg and Murchison believe that twelve to forty-eight hours must elapse before obstruction of the bile-ducts and the appearance of the jaundice occur "The enormous change which the circulation of the liver undergoes about the time of birth constitutes the most probable explanation of the relation between the onset of jaundice and that event" So even if one accepts a congenital malformation as the cause for the obliteration of the ducts, one can explain the lapse of time between the birth and the period of onset of the jaundice by the fact that the cells of the child's liver which had long ceased to secrete bile owing to the permanent blocking of the ducts, are stimulated by the sudden change in the circulation to return to their natural function of bile production

2 Character and Progress of the Jaundice The icterus is always progressive and sooner or later becomes marked, being of a deep greenish



hue — in our case of that peculiar coppery tint that is actually offensive to the eye. Sometimes the degree of jaundice appears to vary from day to day and in some cases it becomes paler before death. It is a curious fact, however, that even when one duct is pervious, the jaundice may be as deep as in a case with complete occlusion.

3 Urine. The urine is always said to contain large quantities of bile pigments except in one case reported where none was found present.

4 Meconium. In some cases it was colored and in others quite white, due, no doubt, to the fact that the occlusion of the ducts occurred at different periods of intra-uterine life. In no case was a dark meconium followed by normal-colored feces, even if the icterus did not develop until much later. Hence one may conclude that the biliary obstruction is always considerably advanced at birth. Further, from this it would appear that the obliteration of the ducts is not due to an arrested development, though there may be a very early obstruction to the lumen of the biliary passages.

5 Stools. The color of the stools will vary with the degree of obstruction, thus, where the obstruction is not complete the stools may be green or brown. Where, however, the obstruction is extensive, the color varies from white to cream and in one of the reported cases and in ours, resembled white lead. In certain of the cases in which there was found post mortem complete obstruction, the stools were noted to have a greenish tinge. The possible explanation of this green color is first, a mixture of the stool with bile-stained mucus, second, the result of the administration of mercury which notoriously produces green-colored stools, and third the influence of microorganisms.

6 Vomiting. This seems of rare occurrence and was noted in but a small percentage of the cases in the literature — 18 per cent in Thomson's series. It was rather a prominent feature in our case, especially in the terminal stages.

7 Hemorrhages. The occurrence of hemorrhages into the skin and conjunctivæ or from the mucous membrane of the nose, gastro-intestinal tract, and from the umbilical cord, has been noted in nearly 50 per cent of the cases. It was absent in ours. This hemorrhagic tendency is similar to that present in all cases of obstructive jaundice in the adult and is always a serious omen but not necessarily fatal in its results. The cause of it is obscure but several possible explanations have been advanced. First, an impoverishment of the blood, that is, a diminution in the ratio of red blood-cells to the fibrin content, second, hemolysis of the red cells by the biliary acids circulating in the blood, third, parenchymatous degeneration of the blood-vessels similar to the change that occurs in the glands and muscles as a result of the bile acids, and fourth, the presence in the blood of ptomains formed in the process of digestion which the diseased

liver is unable to render innocuous Thomson discards the first three possibilities and accepts the fourth as the most plausible

8 Emaciation Contrary to what one might expect, this is not an early symptom, which, as Thomson suggests, shows that the presence of bile is not very necessary for ordinary digestion If, however, the child lives long enough, emaciation will develop, due to the secondary hepatic changes and consequent interference with the proper assimilation of fat, and other important functions

9 Duration of Life If one excludes the patient who died from umbilical hemorrhage — a not uncommon accident in these cases — the majority lived more than one month after birth One only was still-born, eleven lived less than a week, eight lived one to four weeks, and fourteen lived from one to four months and sixteen more than four months after birth Our patient, who lived ten weeks, is, therefore, not remarkable in the duration of life in spite of the extensive obliteration of the biliary tracts Lavenson found in his series of sixty-two cases that only three patients lived longer than eight months — two until the ninth and one until the eleventh month

### III GROSS AND MICROSCOPICAL ANATOMY

Ascites was pronounced in two of Thomson's series while peritoneal adhesions were found in five others The liver was generally but not always increased in size One case of an atrophic liver was noted The color was usually dark green and often of a peculiar morocco-leather appearance, owing to the dark green color and the finely granular surface The consistency was tough, suggesting the presence of an increased amount of fibrous tissue The portal vein and vessels were normal except in four cases which were probably luetic in origin, and in which there was obliteration of the portal vein

The condition of the bile-passages and gall-bladder can best be described under four groups In the first group there was no passage from the liver to the duodenum, though the gall-bladder and cystic duct were patent In the second group a passage was present from the liver to the duodenum but no cystic duct or anything to represent the gall-bladder In the third group both cystic and hepatic ducts were obliterated Our case would be included in this division which is, by far, the commonest In the fourth group there was obliteration at a variable point below the juncture of the cystic and hepatic ducts

There is a great variety in the secondary changes in the external excretory apparatus and there appears to be no relationship between the presence of jaundice at birth and the nature of the malformation Thus, the most severe malformations occurred in cases which lived for several months A dilatation of the canal above the point of obliteration was not

invariably present but may exist to an enormous extent (e g, Miller's case<sup>10</sup>) The obliterated duct may remain as a fibrous cord or entirely disappear If the gall-bladder exists, its contents vary from a peculiar thick, syrupy bile to a clear watery fluid The latter is true if the child has lived more than a month

In Thomson's series the spleen was usually found enlarged, as was observed in ten of twelve cases in which its condition was noted Sometimes it was very large



Fig 1—Low-power view showing intralobular and perilobular connective tissue increase The small black areas in one portal space are inspissated bile in bile ducts

*Histological Anatomy*—A microscopical examination was made in but nine of the earlier cases, in all of which, however, a hepatic cirrhosis was present, while masses of inspissated bile were noted in the ducts and liver-cells In the more recent cases a more or less complete histological study has been made The chief point of interest is that at autopsy at least, the liver shows a more or less advanced cirrhosis of the mixed type with the biliary cirrhotic features predominating The detailed picture is well illustrated by our protocol

## IV PATHOGENESIS

This is one of the moot questions in the literature of this subject. Thomson, Rolleston and Lavenson, as representatives of the most distinct views, will be most freely quoted by us. As pointed out by Lavenson, one can divide the theories advanced into two classes: (I) that which considers the disease as a primary involvement of the ducts, (II) that which considers it as a primary involvement of the liver, i. e., a cirrhosis.

*I The Theory of a Primary Involvement of the Ducts*—In support of the view that the obstruction of the duct is the primary condition and the cirrhosis the result of the ensuing biliary stasis, Lavenson advances the following facts:

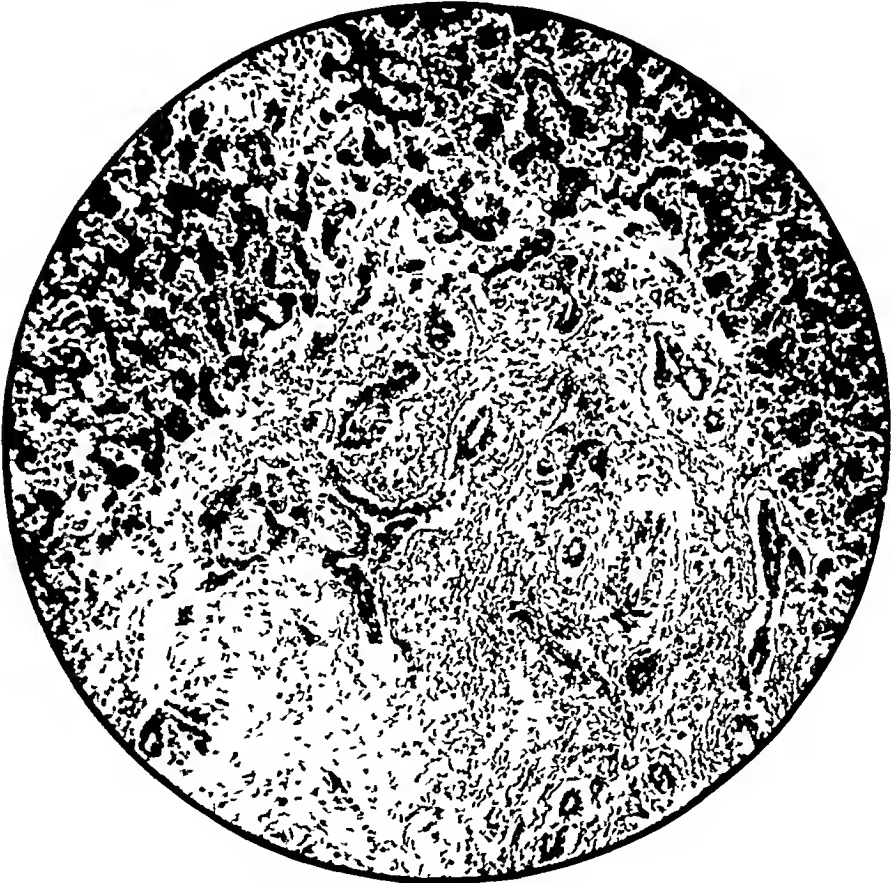


Fig. 2.—High power view, showing proliferation of bile ducts in a portal space.

First, in both adults and children biliary stasis results in the same chain of events and the same pathological findings as are present in the cases under discussion.

Secondly, Steinhaus, Pick, Lannaeq, Gerhardt, Beloussow, Harley and Tsunoda<sup>23</sup> have shown experimentally in animals the same changes in the liver as are found in cases of biliary stasis in man.

Under this head the possibilities to be considered are (1) an anomaly of development, (2) organization of a non-specific inflammation either within or without the ducts, (3) syphilis.

1 *The Theory of Congenital Malformation*—This theory originally was supported by Thomson,<sup>1</sup> who believed in a primary congenital malformation of the duct which resulted in narrowing of the lumen and predisposed to a catarrh, and so to a blocking and finally caused the complete obstruction of the duct. This, in turn, led to a biliary cirrhosis of the liver. He believed that the obliteration was usually complete at an early period of intra-uterine life. He pointed out that the appearance of jaundice in several members of a family supported this congenital developmental theory and explained the fact that when the onset of jaundice was not contemporaneous with the blocking of the duct (i. e., did not occur

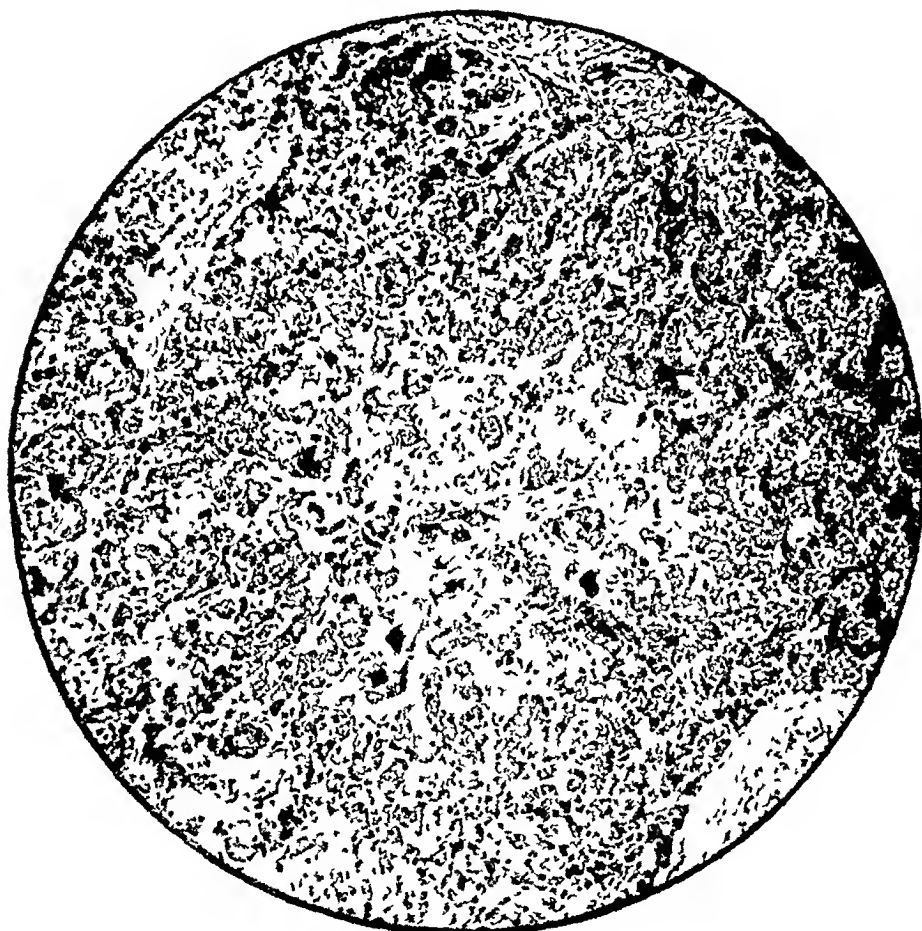


Fig. 3—Medium power view of one anatomical lobule, showing central increase of connective tissue and distended bile capillaries

until several days after birth) it was due to circulatory changes that occurred in the liver at birth

Weber believes that some cases of congenital obliteration of the bile ducts are due to a primary developmental malformation similar to that in congenital valvular disease of the heart. But in another paragraph<sup>11</sup> he writes "These congenital changes were doubtless partly inflammatory in origin and as usual were unaccompanied by congenital defects elsewhere in the body"

Bushnell<sup>7</sup> and Simmonds<sup>9</sup> support this view of an error of development. Fuss and Boye also "believe that the absence of any cystic enlargement of the gall-passages and the enormous hypertrophy of the liver-tissue speak rather for a developmental error. The liver changes may be secondary to bile stagnation, analogous to the experimental cirrhosis from constriction of the common duct." But they also admit "another possibility is a primary liver disease which descending produced an obliteration of the ducts."

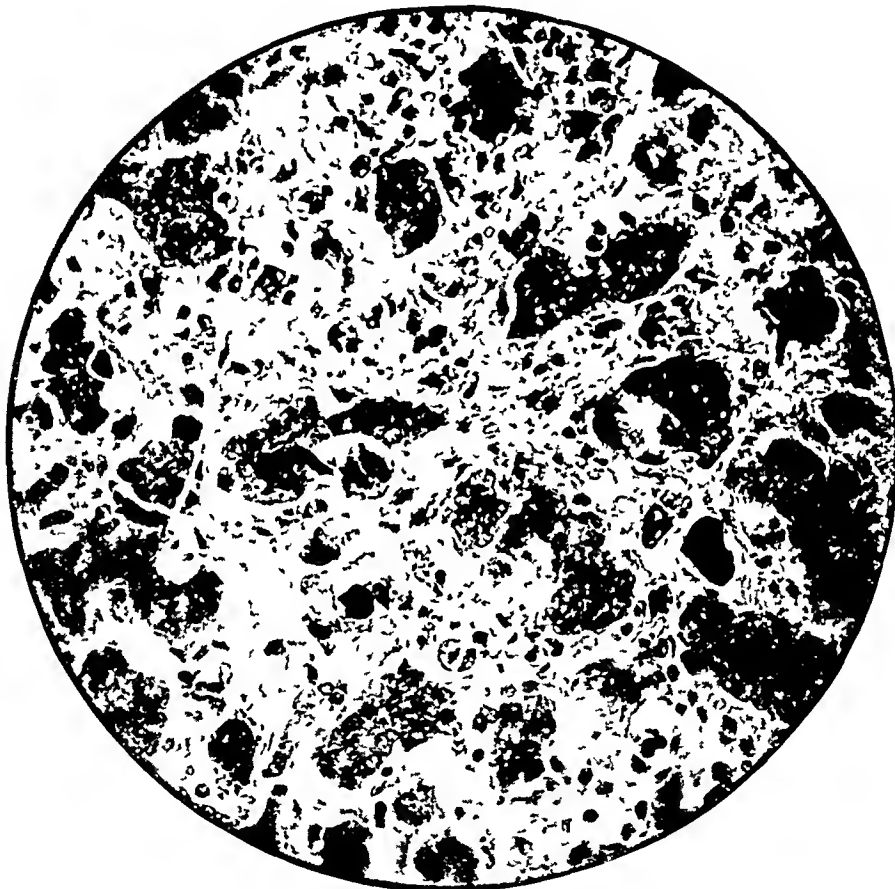


Fig 4—High power view of center of Figure 3. Shows atrophied liver-cells and inspissated bile in the connective tissue. Rupture of the bile capillaries and atrophy of the liver cells are the probable factors leading to the liberation of the inspissated bile.

Thomson's original theory was carried still further by Lavenson,<sup>3</sup> who believes that the atresia is primary and that the cirrhosis results from the biliary stasis. He states that the fibers of Renak (the offshoots from the embryonic solid cord that buds out of the primitive gut to form the liver and hepatic ducts) remain solid instead of developing a lumen as they do normally. Another possible explanation is a faulty union of the two rudimentary portions of the ductus hepaticus and ductus choledochus. This receives support in a certain proportion of the cases in which the obliteration is found at the point of union of these two portions.

Furthermore, the occurrence of other undoubted anomalies of the liver and its appendages (e g, entire absence of the gall-bladder, cystic duct, caudate and Spigelian lobes, transposition of the portal vein and artery<sup>1</sup>) and occasionally congenital defects in other portions of the body (e g, situs inversus,<sup>17</sup> cystic liver and kidneys, patent ductus Botalli,<sup>5</sup> and even absence of right hand and ulna) "lead one to believe that a large percentage of the cases are a result of a congenital defect of development" Further, Lavenson considers that "the term 'atresia of the bile-duct' better expresses the existing condition than 'obliteration of the bile-ducts' "

Though, as we shall see in the next paragraph, Thomson repudiated for a time the theory of congenital malformation in his last article<sup>20</sup> he has adopted again his original doctrine and wrote "I am inclined to return to the view I formerly held as to a relative narrowing of the bile-ducts of developmental origin being probably the primary cause of all the other changes "

2 *Organization of a Non-Specific Inflammation of the Ducts*—In his second article,<sup>18</sup> Thomson admitted if the obliteration were due to an arrest of development, the former would occur at the same site in the majority of cases This is not the case The same would be true if it were due to a local stimulus within the tube like a calculus, for example, as was found in two instances<sup>20</sup> He therefore advanced another suggestion namely, that irritative substances which were present in the bile set up a descending cholangitis which resulted in interference with the passage of the bile and finally in biliary cirrhosis just as occurs in animals in which the common duct is tied

We quite agree with Lavenson when he states that the preexistence of a non-specific inflammation is impossible to either deny or affirm, for when the case comes to autopsy the acute process is replaced by fibroid changes not characteristic of any form of inflammation Nevertheless, the relative infrequency of a true catarrhal jaundice in infants is against this theory

Obliteration of the ducts from without by adhesions resulting from a fetal peritonitis may be the cause of a certain number of these cases according to both Thomson<sup>1</sup> and Rolleston<sup>14</sup> The former found in five of his series, peritoneal adhesions present in the neighborhood of the ducts implicating the blood-vessels, and believed that peritonitis is a common occurrence in fetal life, though he frankly admits it is most often due to syphilis It seems more probable, however, that the peritonitis is a result and not the cause of the obliteration of the duct

3 *Syphilis*—Petit and Merle<sup>13</sup> regard the process not as an arrest of development but as an inflammatory degenerative process of the biliary tract in intra-uterine life, probably syphilitic in origin in spite of the

absence of a history of lues They term this condition fetal angiocholitis M and R C Ferriard<sup>14</sup> also support this view and make use of the same term

While one must admit that congenital luetic hepatitis and cholelithiasis may simulate the disease under discussion (e g, Beck, Rolleston<sup>15</sup> and Simonini<sup>16</sup>) the absence in the latter of the numerous definite stigmata of syphilis and the Wassermann reaction make this theory untenable

*II The Theory of a Primary Congenital Cirrhosis*—Rolleston put forward this hypothesis and advanced in support the following facts

A The almost constant occurrence of cirrhosis in these cases in infancy as compared with the rarity of cirrhosis of the liver following obstruction of the bile-ducts in later adult life

B The large size of the liver which resembles the liver of biliary hypertrophic cirrhosis In adults, on the other hand, simple obstruction of the bile-passages causes at first an enlargement of the liver and subsequently atrophy

C The large size of the spleen in the infant a phenomenon not encountered in the uncomplicated biliary obstruction of the adult

D "The fact that in some instances several cases of this rare disease have occurred in the same family"

To explain the occurrence of the biliary cirrhosis in the new-born child, he writes that "poisons pass by the blood from the placenta to the fetus by the umbilical vein Some of this toxic blood produces ordinary portal or multilobular cirrhosis Some of the blood, however, passes directly into the general circulation by means of the ductus venosus, hence by the hepatic artery to the liver where it will set up in the small intra-hepatic bile-ducts a cholangitis and monolobular cirrhosis resembling that seen in hypertrophic biliary cirrhosis" In this way both a portal and biliary or what is termed a mixed cirrhosis is produced This cholangitis descends to the larger ducts Now, as the bile-ducts are extremely small at birth, any inflammatory changes will, on account of the small size of the lumen, produce a stenosis much more readily than in later adult life He not inaptly compares this descending obliterative inflammation of the larger extrahepatic ducts with the processes at work in an obliterative appendicitis

Rolleston frankly admits that against this theory is the unanswerable fact that the poisons which cause the condition in the liver of the child must circulate in the mother, and that she should show evidences of its influence He further remarks that it is possible that there are several conditions at present included under the title "congenital obliteration of the ducts," and that some cases are due to constriction of the duct by a localized peritonitis and deserve the title of "congenital obliteration of



the ducts" better than those cases which are intimately associated with cirrhosis. Emanuel,<sup>8</sup> among others, supports this theory because of the fact that there was a fibrosis of the pancreas in his case without much secondary involvement of the pancreatic ducts, in other words, there was a toxic fibrosis of the liver, spleen and pancreas.

Lavenson strongly attacks Rolleston's views and meets each argument by a counter one.

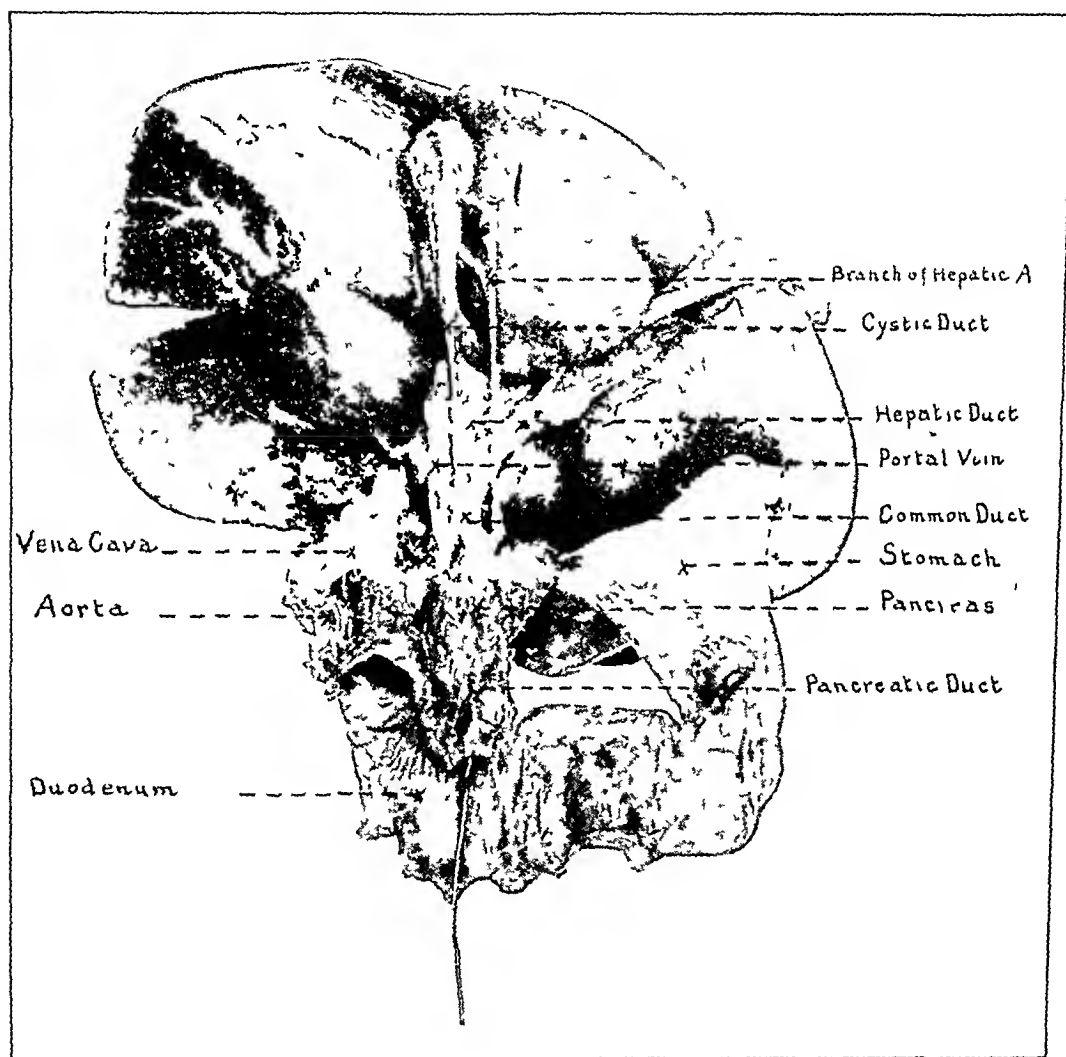


Fig 5—Obliteration of the bile ducts

A. Thus he points out that the statement that cirrhosis following biliary obstruction in the adult is rare, cannot be accepted in view of the fact that Mangelsdorf<sup>22</sup> and Ford were able to collect reports of some 208 cases and that no doubt many cases occur and are not recorded. Further, Lavenson asks why, if Rolleston's contention be true, is not biliary obstruction more common in Hanot's cirrhosis of adults? Another important point is that Lavenson found that in twenty-four of sixty-two cases the obstruction was in the duodenal portion of the bile-duct while

the hepatic portion was patulous. Lastly, some patients who died shortly after birth showed only the earliest stages of cirrhosis because the biliary stasis had not existed long enough.

B. Lavenson admits that in the condition under discussion, the liver is large just as it is in Hanot's biliary cirrhosis, but it is also true of cirrhotic livers following biliary obstruction in adults, and quotes the following: "The livers in these cases of obstructive cirrhosis are greatly enlarged with a rough jaundiced surface and considerable perihepatitis."<sup>22</sup>

C. To controvert this point he cites from Rolleston's text-book in the section on cirrhosis from biliary obstruction in adults: "The spleen is sometimes small or of normal size but in cases where considerable fibrosis of the liver coexists with obstruction of the larger ducts, there may be a considerable enlargement (of the spleen), though not to the same degree as in hypertrophic biliary cirrhosis."

D. Lavenson would accept only Binz's cases as examples of the disease occurring in the same family. He rejects the other cases on the grounds of insufficient data (West's two cases, Thomas, Aikwright, Bloomfield<sup>23</sup> and Pearson). Lavenson concludes with the remark: "There is little or no support of the view that the obstruction is secondary to the cirrhosis."

The writers agree with Rolleston,<sup>2</sup> Griffith<sup>21</sup> and Peck<sup>12</sup> that there is probably some truth in all the theories advanced, some cases may be due to an anomaly of development, others to a simple inflammation of the ducts, and still others to a primary congenital cirrhosis. No one theory will suffice for all the cases reported under the title of "congenital obliteration of the bile-ducts."

## V DIAGNOSIS

1 *Simple Icterus Neonatorum*—This condition is of relatively frequent occurrence and was present, according to Holt in 300 of 900 consecutive births at the Sloane Maternity Hospital. The intensity of the jaundice is usually slight and it rarely persists even in the most severe cases for more than two weeks. Furthermore, the color of the stools remains unaltered and, as a rule, the skin of the child even in the absence of treatment, soon returns to a normal color.

2 *Congenital Syphilitic Hepatitis*—In this condition, apart from the presence of other luetic stigmata in the child or the history in one or the other parent of a venereal infection, there may be a great enlargement of the liver and occasionally ascites, but jaundice is rare and then usually very slight in character. Post mortem, there is found a great liability to an obliteration of the portal vein.

3 *Septic Jaundice*—This may exist in association with phlebitis of the umbilical vein. This is a severe and very fatal form in which hemorrhages from the cord are the prominent feature.

4 *The Ictère Splénomégalique of the French*—This rare disease occurs in older children and is associated with a gigantic spleen, ascites, marked enlargement of the abdominal veins, deep jaundice, clubbing of the fingers, and stunting of the general growth

#### VI TREATMENT

Medicinal treatment is certainly valueless. Calomel, gray powder and saline purgatives have been tried by all but, naturally, without success. Surgical procedures cannot offer much hope except in those cases in which the obstruction is incomplete and confined to the lower or duodenal end of the ducts. In such cases a union between the patulous portion of the duct and some loop of the intestine might be procured. Giese, J. L. Morse and Murphy,<sup>20</sup> and Putnam have reported cases in which operative measures were tried but without success.

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# DUODENAL DIAGNOSIS X-RAY CONSIDERATIONS

## A TECHNIC FOR FLUOROSCOPY<sup>\*</sup>

E H SKINNER, M D

KANSAS CITY, MO

The estimation of gastro-intestinal pathology is being placed on a safer basis than subjective symptomatology. The stomach may be the barometer of digestive function but not so frequently the site of the pathologic conditions. Mayo<sup>1</sup> says that "the stomach has been credited with a host of diseases which it never possessed and has received an amount of treatment for supposititious conditions that is little credit to the medical profession. These mistakes have been due mainly to fundamental misconceptions of the function of the stomach, its relation to diseases in general and especially to those of the digestive tract. Mistakes in diagnosis are more often the result of lack of examination than a lack of knowledge. Prolonged laboratory examination and investigation has been productive of much harm. A scientific but deadly delay."

The primary etiological factor in duodenal ulcer is as obscure as that of gastric ulcer. Predisposing conditions and contributory causes depend on interference with normal function in the duodenum and are of wide latitude. Mechanical and chemical causes are dependent on the motility of the stomach and duodenum and on alterations in the pyloroduodenal anatomy. Most duodenal ulcers are found at that point which receives the impact of the acid chyme as it is ejected from the pylorus. The duodenal preference is an alkaline reaction, and the forcible mechanical contact of chemically disagreeable ejecta could do much to break down a normal or weakened resistance. The control of the pylorus is extremely delicate at the best. The rate of the pyloric outflow is governed by the rapidity with which the ejected acid chyme is neutralized by the alkalinity of the duodenal secretions. The presence of acid in the pyloric antrum promotes the opening of the pylorus, but the presence of this acid content in the duodenum immediately causes the pylorus to close. The pyloric function is more under the control of the duodenum than the stomach (Mayo).

The greater frequency of duodenal ulcer in men may be dependent on the fact that the first or ascending portion of the duodenum is higher in

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<sup>\*</sup>From the Radiological Department of the Kansas City General Hospital

1 Mayo, W J. Diseases of the Stomach and Duodenum from a Surgical Standpoint, St Paul Med Jour, 1911, LVII, 1, Ulcer of the Duodenum, Jour Am Med Assn, 1908, LI, 556

men than in women, so that the alkaline secretions do not reach or rise as high to neutralize the acid chyme with physiological rapidity. Duodenal ulcers usually occur above the bile-ducts, are single and on the upper circumference, and are more likely to involve the pylorus and stomach than to progress in the opposite direction.

The first or superior portion of the duodenum may be regarded as a physiological part of the stomach. The similarity in the symptoms of gastric and duodenal ulcers also warrants this view. Both Schwarz<sup>2</sup> and Holzkecht,<sup>3</sup> by the use of the fluoroscope and bismuth suspensions, noted that the food when ejected from the stomach remained for some little time in the superior or first part of the duodenal segment before advancing, at a comparatively rapid rate, through the remaining duodenal canal. Holzkecht calls this first duodenal segment the *Pufferraum* or teasing-room. By the fluoroscope he finds that this portion has no peristalsis normally. It acts like a storage-room for the chyme as it is ejected from the pylorus by the peristalsis of the antrum. It can hold quite an amount of chyme and does not rapidly pass this on unless its capacity is taxed, when it permits the surplus to be passed on in small coin-sized masses. These masses normally are not sharply defined by the fluoroscope but they may be distinguished as small masses, not nearly as large as the lumen of the duodenum, and they follow one another every few seconds, resting momentarily at intervals.

Considering that the first part of the duodenum has practically the same functions as the cardiac portion of the stomach, that of a reservoir, we may apply the principles of gastric fluoroscopy to duodenal diagnosis. It is easier to obtain fluoroscopic information regarding the late pathological changes produced by duodenal ulcerations, such as strictures and stenoses, dilatations, diverticula and hour-glass duodenums. In these late manifestations of pathology the bismuth suspensions cast characteristic shadows, the strictures and stenoses prevent the rapid or normal progress of the bismuth, and it dams up according to the degree of the stenosis or dilatation. If the dilatation is not dependent on a stenosis but merely is due to a lack of tonicity in the musculature, we would note a tardy progress of the bismuth through the dilated portions, and the distinct line or contracted area of a stenosis would be absent. In diverticula the pocket might become filled with the bismuth and so demonstrated as an abnormal shadow without the lumen of the duodenum but contiguous thereto. In all these late or chronic diseased conditions, it is not necessary but it is advantageous to employ special means of filling the duodenum with bismuth emulsions or suspensions. Bismuth and water pass rapidly through the pylorus of a fasting patient, and with

<sup>2</sup> Schwarz. Berl. Klin. Wchnschr., 1908. No. 21, Abstr. in Fortschr. d. Geb. d. Röntgenstrahlen, 1908, vii, 435.

<sup>3</sup> Holzkecht. Deutsch. Ztschr. f. Chir., 1911, cv, 54.

even a mild degree of pyloric spasticity or physiological closure of the pylorus, the suspension would fill up the duodenum before the duodenal pathology permitted the passing of such suspensions beyond. It is in the acute spasmodic functional disturbances of motility that the artificial filling of the duodenum is necessary.

This artificial filling may be accomplished by using a Gross duodenal tube, which is a small rubber tube tipped with a small ball. For this fluoroscopic examination it is necessary to substitute a lead ball for the aluminum one that Gross first devised, so as to obtain an image by the Roentgen ray. The patient swallows the ball and tube, it passes the pylorus and then the bismuth suspension is poured directly into the duodenum, as there are small holes for the exit of the fluid, just above the small ball.

Barclay<sup>4</sup> has frequently noted by ordinary fluoroscopy that a shadow which is separated from the pylorus persists beyond the pylorus and remains uninfluenced by the stomach peristalsis. There was usually a normal stomach shadow but a violent peristalsis. The pylorus opened more frequently and the gastric contents passed more rapidly, so that the stomach emptied itself in a short time, perhaps in one-half hour. Whenever he found this normal stomach shadow with excessive peristalsis passing the food rapidly, he considered it diagnostic of duodenal ulcer.

Distention changes in the duodenum and small intestines may be due to obstruction of the ileum. The obstruction of the ileum may be due to kinks produced by its mesenteric attachments, or to an anchored appendix, or to the weight of a loaded cecum which lessens the lumen of the ileum as it passes over the pelvic brim. Lane<sup>5</sup> has been unable to satisfy himself regarding the mechanism of this duodenal distention. At first he thought that the ileac obstruction dammed back the intestinal contents but that this could only be a reflex cause, as the jejunum emptied itself rapidly. Later he considered the distention secondary to the compression or obstruction of the third part of the duodenum by the strain exerted by the mesentery of the jejunum. Jordan<sup>6</sup> has always been able to demonstrate this duodenal distention in Lane's cases, by the fluoroscope and bismuth suspensions. The bismuth would advance normally to the third portion of the duodenum but here it halted, and only after four and nine hours was the obstruction seen to relax and eject some bismuth. During the time that the duodenum was filled, active and often violent peristalsis was seen in the walls of the duodenum. The stomach itself emptied normally, although usually it was dilated and elongated.

Lane and Jordan report four cases in which they demonstrated the distention of the duodenum by the fluoroscope and bismuth. They fre-

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<sup>4</sup> Barclay Arch. Roentgen Ray, 1910, xv, 174

<sup>5</sup> Lane Surg, Gynec and Obst, 1911, xii, 222

<sup>6</sup> Jordan Surg, Gynec and Obst, 1911 xii 226, quoted by Lane

quently found duodenal ulcer associated in this class of cases. Operative interference disclosed usually a vertical downward pull on the commencement of the jejunum with a torsion which rendered evacuation of the duodenal contents difficult. The cecum was frequently found fixed by adhesions in the iliac fossa and the iliac obstruction was purely static, owing to resistance of the bulk of the pelvis.

Holzknecht diagnosed five cases of duodenal stenosis by the fluoroscopic examination. The duodenum filled up behind the stenosis, so that the walls were in sharp contrast. The duration of the filling depends on the depth of the stenosis and the degree of the disproportion between the narrowness of the stenosis and the peristaltic strength of the stomach and duodenum, and on the mass of the ingesta in the duodenum. The duodenum, when filled behind a stenosis, exhibits worm-like convulsive contractions without visible effect on the mass, i. e., there is no outpouring through the stenosis. This peristalsis of the duodenum occurred at rhythmical intervals of about seven seconds and lasted about two or three seconds. Where there was a high degree of stenosis there appeared to be an atony of the dilated duodenal walls, probably owing to lack of compensation in the musculature. The degree of the stenosis was estimated by the length of time during which bismuth contents remained in the duodenum, which varied from a short time in spastic conditions to twenty-four hours in organic stenosis.

Crane<sup>7</sup> recently called attention to the possibility of outlining the head of the pancreas, or estimating its size by plotting the curve of duodenum as the duodenum encircles the head of the pancreas.

#### AUTHOR'S TECHNIC

The method of introduction of the Gross duodenal tube has been described fully by Gross.<sup>8</sup> Briefly, the small tube with a lead ball at the end is swallowed about fifteen minutes after the patient has taken a glass of milk. The patient takes an easy position recumbent on the right side with the hips elevated. After about one-half to one hour the patient is fluoroscoped to see if the ball has passed the pylorus. A small amount of bismuth and water may be given (not through the tube). If the tube is in the duodenum it will appear independent of this bismuth stomach shadow. When it is determined that the lead ball at the end of the tube has passed the pylorus and is in the duodenum, a suspension of bismuth in water (one-half ounce of bismuth oxychloride to 6 ounces of water) is funneled into the tube, and thus it reaches the duodenum independent of pyloric activity.

7 Crane. *Tr. Am. Roentgen Ray Soc.*, 1910. Reference from *Am. Quart. Rontgenol.*, 1910, ii, 269.

8 Gross. *Duodenal Ulcer*, *Jour. Am. Med. Assn.*, 1910, liv, 1365.

The patient, just previous to the injection of the bismuth suspension through the tube, is placed on the simple apparatus illustrated in Figure 1. The patient is brought to a horizontal position on the right side, as in Figure 2 just before the suspension is introduced, so that the duodeno-

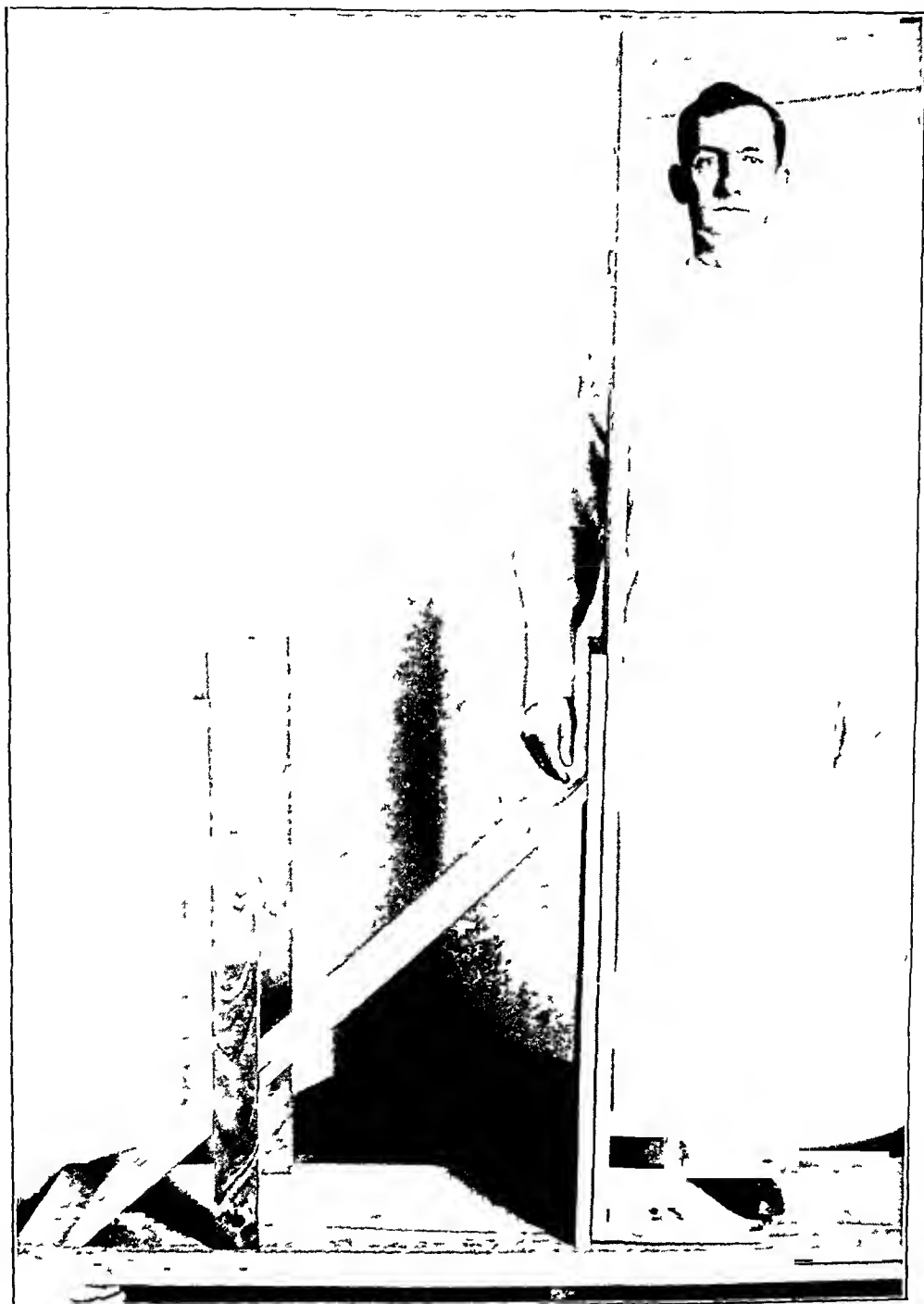


Fig 1 —Apparatus for use in fluoroscopy

jejunal junction will be at the highest point and the duodenum will have the position of an upright U. We are accustomed to use this simple apparatus with a Beclere fluoroscopic stand.



This method of filling the duodenum lends itself to the estimation of duodenal pathologic conditions, especially in cases in which there is a stenosis or interference with the peristalsis. It will usually be found that a peristaltic wave will not pass over an erosion or ulcerated area of the duodenum, rather will it incite a spastic contraction at the site of the ulcer. For outlining the head of the pancreas this method of filling the duodenum would be quite useful, as the bismuth-filled duodenum encircles the head of the pancreas.

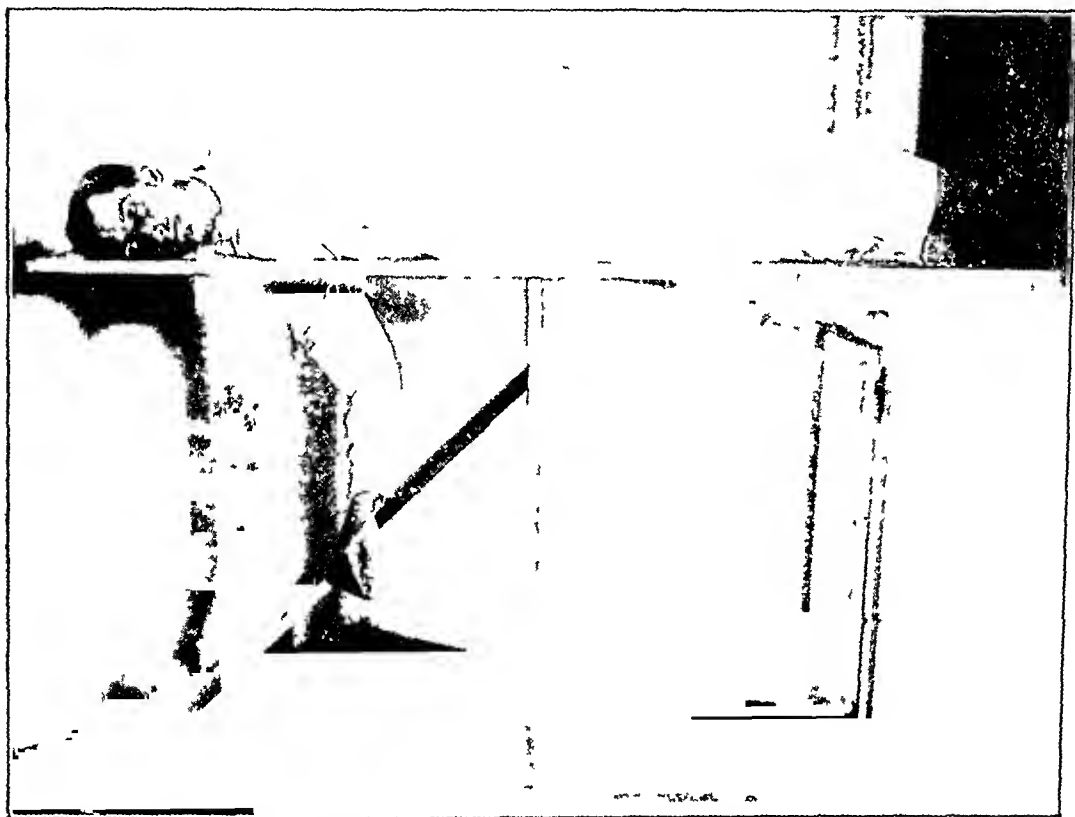


Fig 2—Patient in second position on apparatus

#### CONCLUSIONS

We have been able to estimate a mechanical diagnosis of duodenal ulcer on the following. When a bismuth-and-water suspension is swallowed by a fasting patient, it readily passes the pylorus into the duodenum (because the acid stomach content is not taken up as when food is offered the stomach, neither is there a closure of pylorus as when a food bolus is swallowed). The stomach appears normal after the ingestion of a bismuth meal (2 ounces of bismuth oxychloride to 13 ounces of porridge of one of the prepared wheat breakfast-foods), but there is a vigorous peristalsis and a rapid emptying of the stomach in as short a time as one-half hour and at least in two hours. The duodenum seems to be sluggish and casts a shadow for a longer interval than usual, but the food

rapidly traverses the remaining portion of the small intestines. By this method of filling the duodenum, as described above, the duodenum may present an hour-glass contraction at the site of the ulcer. Usually the duodenum is sluggish and does not exhibit any pronounced peristalsis. When the duodenum is filled and pressure is made at the outer curve of the duodenum as shown by the shadow, the patient usually experiences some pain or discomfort. We place the greatest weight on the rapid emptying of a stomach that exhibits the usual normal J-shaped shadow and a vigorous peristalsis.

1018 1020 Rialto Building

## AMEBOID MOVEMENTS IN MACROCYTES AND MEGALOBLASTS \*

ROGER S MORRIS, M D , AND WILLIAM S THAYER, M D

ST LOUIS

BALTIMORE

Since the observations made by one of us<sup>1</sup> of ameboid movements in a megaloblast, the opportunity has presented itself to study the fresh blood of five severe anemias

In three of the bloods examined by us, ameboid motion was striking not only in many of the megaloblasts but also in the macrocytes. The absence of ameboid activity in the two remaining cases was probably attributable to the almost complete lack of unusually large cells in the blood. (For the blood findings, see the accompanying table.)

Two of the bloods (Cases 1 and 2) were demonstrated to the class and the changes described below were observed by practically all of the ninety-odd students. In addition, we made prolonged observations on each of the bloods. Our specimens were sealed at once with petrolatum to prevent drying and to avoid currents in the plasma as far as possible.

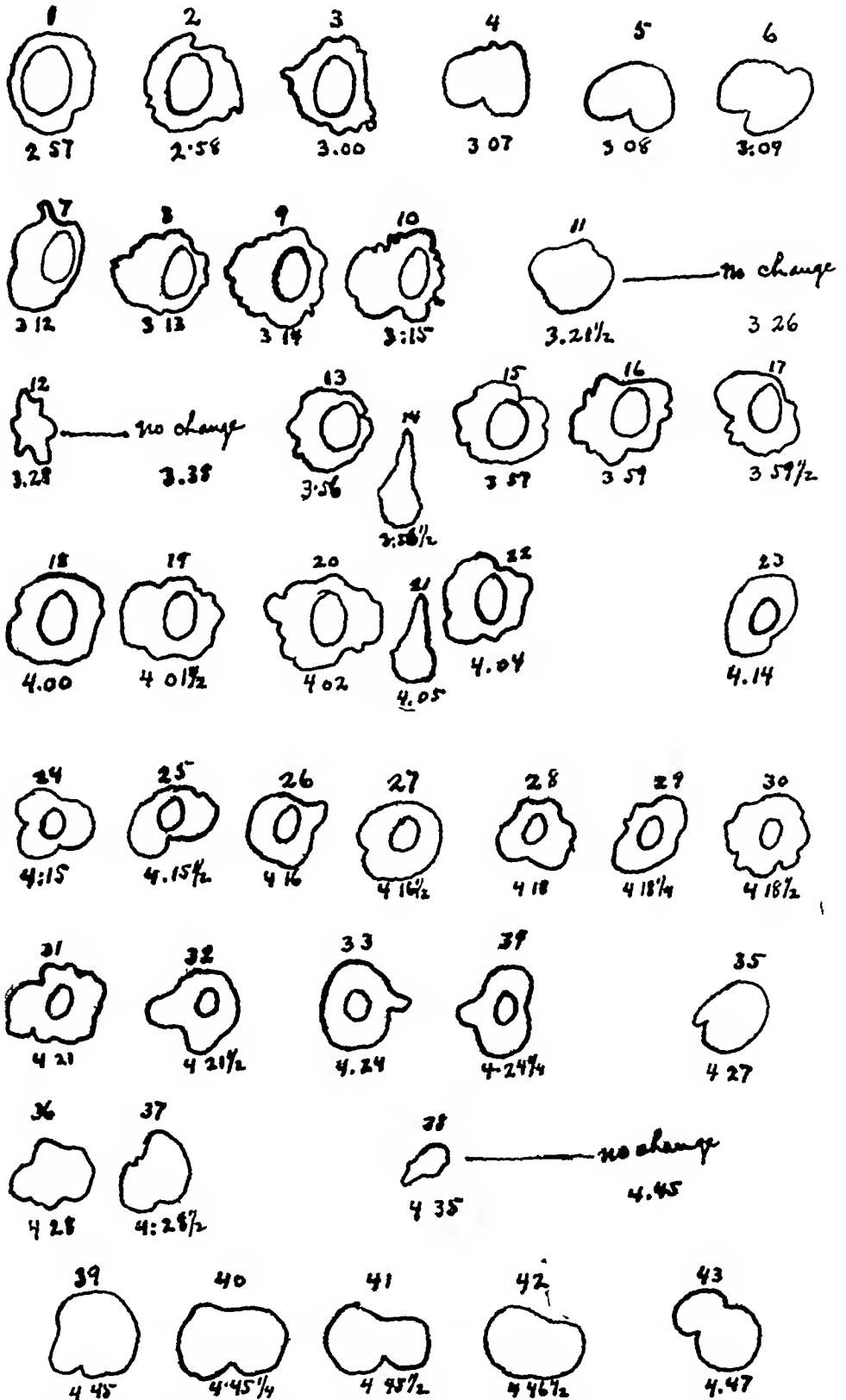
In Case 1, preparations of the blood were studied during a megaloblastic crisis. The megaloblasts were quite numerous and were so frequently irregular in outline that they were found without difficulty with low magnification (Leitz ocular No 3, objective No 3). When examined under the oil immersion they often showed a striking change in form (Figs 1-3, 7-10, 13-17, 18-22, 23-34, 51-66, 67-97, 103-105, 126-138), and at times, though not often, the change was so rapid that the successive alterations in shape could not be sketched. The phenomenon consists essentially of a change in form due (1) to small, often numerous, serrations in the outline of the cell which may later be smoothed out or which may develop into a large, prominent projection or pseudopod, or (2) to the protrusion of one or more blunt, rounded pseudopodia, often large, which may be accentuated by a constriction at the base, or (3) to a combination of these appearances at one time in the same cell. At times rather deep indentations appeared at one or more points on the rim of the cell. Sometimes these nicks appeared to be bridged over in part by a delicate, colorless film, showing at times a slight wrinkling, as if the coloring-matter were at this point retracting

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\*From the Clinical Laboratory the Johns Hopkins University and Hospital

1 Thayer, W S. The Ameboid Activity of Megaloblasts, *THE ARCHIVES*  
*INT MED*, 1911, vii, 223

All drawings are made from specimens of fresh blood with Lertz ocular No 3, objective 1/12" oil immersion. The drawings are not made to scale. The numerals above each sketch denote the number of the sketch, those below, the time intervals.



Figs 1 to 3—Case 1—Megaloblast. Figs 4 to 6—Case 1—Macrocyte. Figs 7 to 10—Case 1—Megaloblast. Fig 11—Case 1—Macrocyte. Fig 12—Case 1—Poikilocyte. Figs 13 to 22—Case 1—Megaloblast. Figs 14 to 21—Case 1—A poikilocyte which showed no change during time of observation. Figs 23 to 34—Case 1—Megaloblast. Figs 35 to 37—Case 1—Macrocyte. Fig 38—Case 1—Poikilocyte (small). Figs 39 to 45—Case 1—Macrocyte.

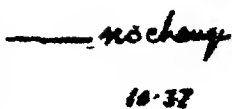
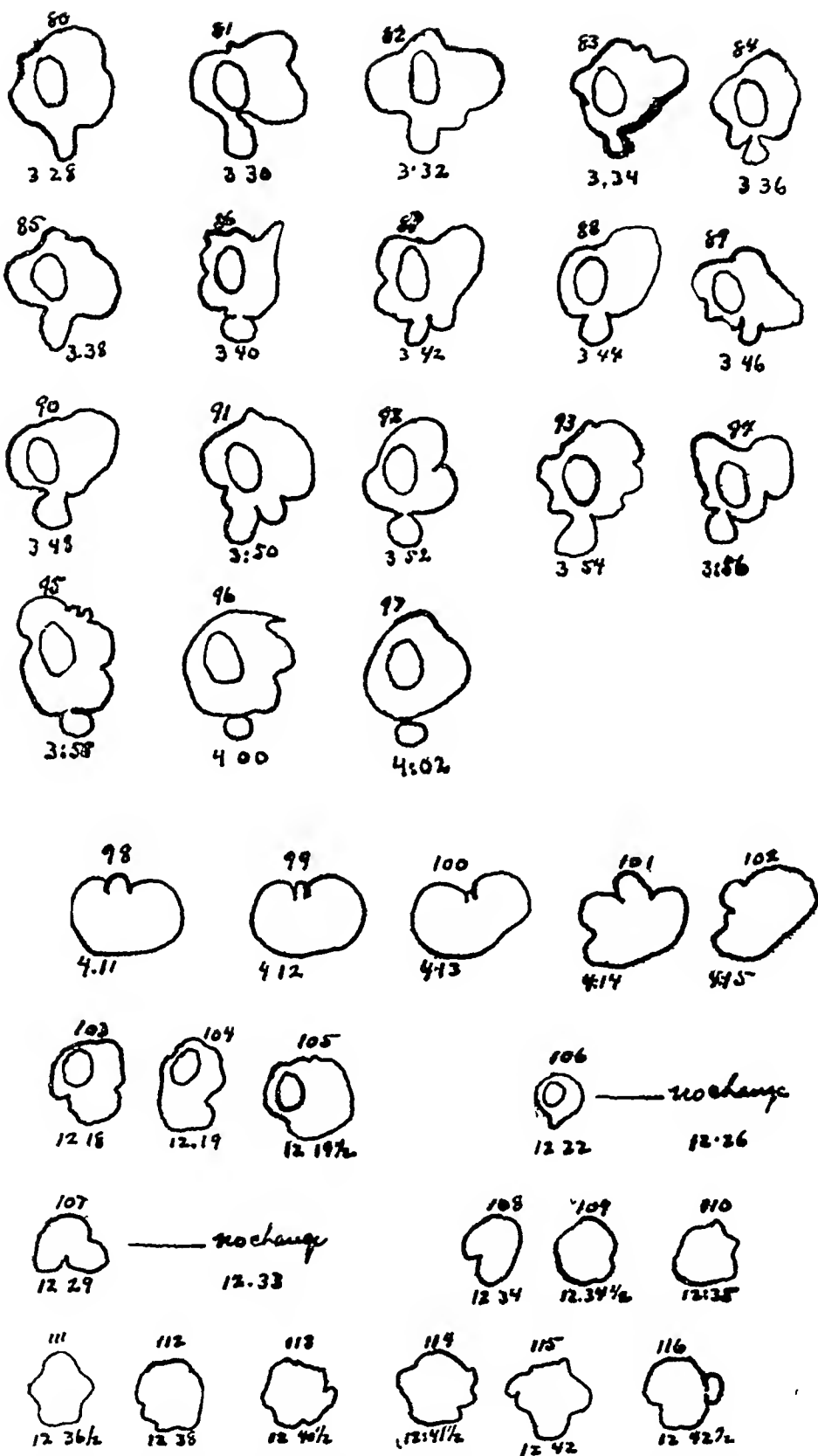
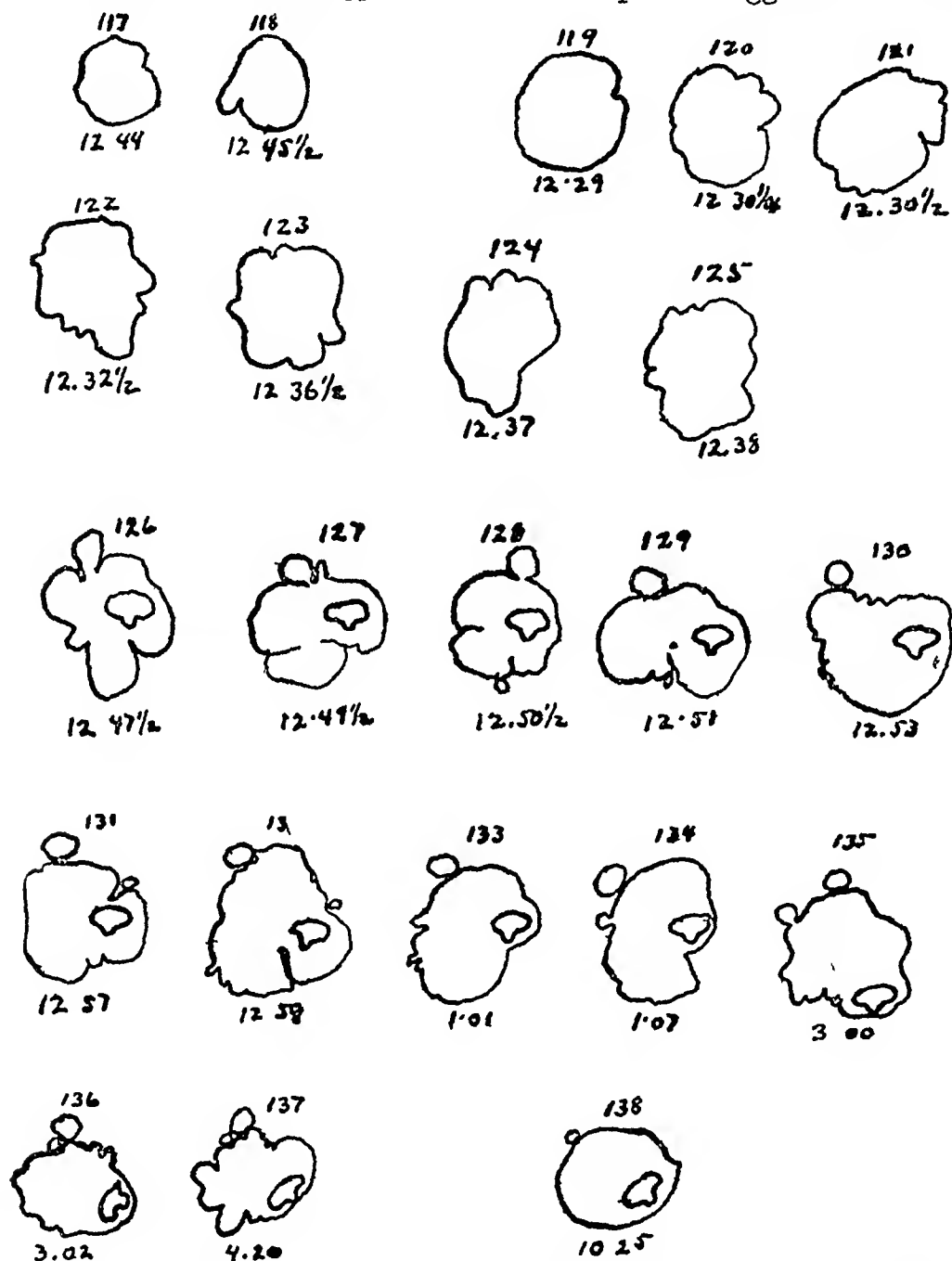


Fig 46—Case 1—Poikilocyte (small) Fig 47—Case 1—Megaloblast Figs 48 to 50—Case 1—Megaloblast Figs 51 to 66—Case 1—Megaloblast Figs 67 to 97—Case 1—Megaloblast



Figs 98 to 102—Case 1—Macrocyte (rather small) Figs 103 to 105—Case 2—Intermediate Fig 106—Case 2—Normoblast Fig 107—Case 2—Poi- kilocyte Figs 108 to 112—Case 2—Macrocyte Figs 113 to 118—Case 2—Macrocyte

from the stroma. Indentations such as these were often obliterated by very sudden movements, the colored substance springing back instantaneously and restoring the former contour of the cell or even forming a slight protrusion. The appearance at these points suggested somewhat



Figs 119 to 125—Case 3—Macrocyte Figs 128 to 138—Case 3—Megalo-  
blast Fig 138—Case 3—The cell shown in drawings 126 to 137, the following  
morning

the appearance of some infected corpuscles in estivo-autumnal malaria in which the brassy-colored protoplasm recedes from the colorless outline of the cell. The malarial cells are, however, often deformed and obviously degenerated. But these motile elements showed no abnormal

change in color or general appearance. No cell, indeed, with a suggestion of crenation or of the ordinary changes of shape observed in poikilocytes showed ameboid motion.

We have not been able to demonstrate propulsive motion in an ameboid cell, which remains practically in the same relative position during several hours' observation. In this respect the ameboid movement of the megaloblast differs from that often seen in the leukocytes. Indeed, the megaloblast protrudes its pseudopodium, only to retract it again. Inclusions or other evidences of phagocytosis in megaloblasts have not been seen.

Examination in Case 2 revealed the identical conditions observed in Case 1. Typical megaloblasts are not abundant, but normoblasts and intermediates are numerous. It is noteworthy that it is only the larger cells (megaloblasts and intermediates) which have shown unquestionable changes of form. In normoblasts (Fig 106) we have not seen such alterations, though they have been looked for with considerable patience. Again, in Case 3, ameboid activity was very striking in the megaloblasts. Not all megaloblasts, of course, exhibit ameboid activity, and this is quite what one would expect from analogy with the leukocytes, some being inactive, others active.

That it is the large cells which are chiefly concerned in ameboid movements we have just seen. Further evidence in support of this fact is furnished by the results obtained in Cases 4 and 5. Here, though the reductions in the number of erythrocytes were quite as great or even greater than in the preceding cases, the absence of very large red corpuscles was conspicuous. In Case 5, in fact, no megaloblasts were seen at any stage of the disease, and they were scanty in Case 4. In neither of these cases was active ameboid motion demonstrable in the red cells.

#### AMEBOID ACTIVITY IN MACROCYTES

The observations just recorded confirm the findings previously reported.<sup>1</sup> In addition, we have observed exactly the same changes in shape in *macrocytes* (Figs 4-6, 35-37, 39-45, 98-102, 108-112, 113-118, 119-125). The rapidity of change may be quite as great as in the nucleated red corpuscles and may present all the variations observed in the latter. There was no discoverable difference in kind or in degree. As in the case of the megaloblasts, not all of the macrocytes exhibit ameboid movements (Fig 11). That non-nucleated cells should do so at all seems strange. But if the motility of the megaloblasts is in reality ameboid—and to the writers there appears to be no other explanation—then there can be no doubt that certain macrocytes, too, are possessed of it. Numerous ameboid macrocytes were observed in the blood of Cases 1, 2 and 3. A single, sluggish, rather small macrocyte was found in Case 5 in the



examination of many specimens, this cell appearing at the time of the blood crisis

To determine the effect of temperature, specimens were examined on the warm stage at body heat. It was impossible to see any difference in the ameboid activity of cells studied in this way and those at room temperature (about 70 F°).

Two specimens from Case 1 were allowed to stand over night, the one in the incubator at 37 C°, the other at room temperature, both sealed, as in all instances, with petrolatum. On reexamination, about twenty hours after the specimens had been prepared, it was found that the red corpuscles were remarkably well preserved, little, if any, laking having occurred, though there were crenation in a few cells and endoglobular degenerations in many. The most striking fact noted was that it was no longer possible, as it had been when the smears were fresh, to select megaloblasts with low magnification, since nearly all of them were now circular or oval in outline and therefore less conspicuous. A sluggish, almost imperceptible change in form was observed in one megaloblast (Figs 48-50), and in one only, though many megaloblasts and macrocytes were watched over considerable periods of time. In Case 3, in a specimen of blood which had been prepared and sealed at 11 a. m., a megaloblast, actively ameboid, was fixed in the field at about 12:45 p. m. It remained very active until 4:20 p. m., when the observations were temporarily interrupted. The following morning at 10:25, the cell was almost round (Fig 138) and the ameboid activity had entirely ceased. This megaloblast showed no endoglobular degeneration and no apparent loss in color. Its nucleus, as is the rule in such cells, showed practically no change in shape throughout the observations (Figs 126-138). In these specimens examined after twenty or more hours, the leukocytes also showed a cessation of ameboid activity, though, unlike the red corpuscles, they frequently retained their irregular shape.

The cells, both megaloblasts and macrocytes, exhibiting ameboid movements were for the most part well colored, many seeming to be richer in hemoglobin than the average cell. A few, paler than the majority of the surrounding reds, were seen to change form, but no difference was determined in the motion of such cells and those more highly colored. No suggestion of crenation was observed in the ameboid cells. That the alterations in shape observed were not the result of osmosis is made probable by the absence of shadows or crenated erythrocytes in the neighborhood of those studied, and, further, by the fact that smaller red cells and many which were large remained immobile.

Many poikilocytes and normocytes were studied. In no case was there the least evidence of change in form while they were under observa-

tion (Figs 12, 14, 21, 38, 46, 107). Rolling of the cells was, of course, excluded. Currents were practically eliminated by sealing the specimens

It occurred to us that it might be possible to demonstrate protoplasmic currents in the ameboid red cells by means of the so-called vital staining methods. It is the young cells which have shown ameboid activity and in these cells particularly, as Vaughan<sup>2</sup> and others have shown, the reticulofilamentous substance is demonstrable. The dyes used were Unna's polychrome methylene blue and neutral red in physiologic salt solution. Of the bloods possessing ameboid red cells, only that from Case 3 was studied in this manner. There was no difficulty in finding macrocytes and megaloblasts with well-stained reticula but in none of them could we see even a suggestion of ameboid movements, though control preparations made at the same time, unstained, contained very active ameboid cells. The neutrophilic leukocytes retained their ameboid activity well in the vitally stained specimens. Though our experiments with vital staining are limited to one case, it seems probable that the staining solutions used abolish the ameboid movements of red cells. This is all the more likely, since there is no description in literature of active movements of the vitally stained particles in erythrocytes, so far as we can discover.

The movements which we have described in macrocytes and megaloblasts were similar to those which were observed in the first case reported, but the protrusion and coalescence of small pseudopods were not so strikingly evident and the similarity of the movements to those of leukocytes not so apparent. The megaloblast originally described was a large, pale form, apparently a very immature cell, while, as has been said, these megaloblasts and macrocytes were all corpuscles of quite the normal color.

As a probable evidence of ameboid activity in megaloblasts, the occasional irregularity in outline seen in stained blood films may be recalled.

That ameboid activity in the red corpuscles may have considerable biologic significance is made clear by recalling the theories advanced to explain leukocytoses. It is not improbable that the "blood crises" are due to an active wandering out of the red cells from the marrow, the result of some unknown stimulus. Should this prove to be the case, it is likely that it will be found to be a departure from the normal, an unusual method of responding to increased normal or pathological stimulus, though for the fetus this may well be physiological. As yet, however, we have been unable to study blood from the fetus.

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<sup>2</sup> Vaughan, V. C., Jr. The Appearance and Significance of Certain Granules in the Erythrocytes of Man, *Jour. Med. Research*, 1903, x, 342.

The counts given below coincide with the dates of examination

CASE 1—E D P, male, aged 41, white, med No 26,575, admitted to the hospital Nov 22, 1910 Diagnosis Pernicious anemia, erysipelas, streptococcus septicemia \*

Dec 1, 1910 Blood examination

Red blood-cells, 900,000

Hemoglobin, 20 per cent

White blood-cells, 8,100

Differential count of 402 cells gave

Lymphocytes	25 7%
Large mononuclears and transitionals	4 7%
Polymorphonuclear neutrophils	59 6%
Eosinophils	1 2%
Mastzellen	0 0%
Myelocytes, neutrophilic	4 2%
Unclassified	4 2%

In counting the leukocytes, 40 megaloblasts, 36 intermediates, and 24 normoblasts were seen

The red cells showed marked anisocytosis and poikilocytosis There were many large cells The stained film revealed polychromatophilia, basophilic granulation, nuclear particles, and Cabot's ring bodies in large numbers Marked signs of regeneration were, therefore, present

CASE 2—J S, male, aged 17, colored, med No 26,868, admitted Jan 25, 1911 Diagnosis Severe anemia (pernicious?)

Feb 21, 1911 Blood examination

Red blood cells, 1,750,000

Hemoglobin, 38 per cent

White blood-cells, 21,000

Differential count of 800 cells gave

Lymphocytes	24 7%
Large mononuclears and transitionals	8 7%
Polymorphonuclear neutrophils	59 0%
Eosinophils	6 3%
Mastzellen	0 7%
Myelocytes, neutrophilic	0 7%

Nucleated red cells were present in the proportion of 350 to 1,000 white cells, normoblasts predominating There were considerable anisocytosis and poikilocytosis Macrocytes were numerous but were not so large as in the preceding case A Romanowsky stain showed much the same changes in the erythrocytes as in Case 1, but to a less degree, though the nucleated forms were more common

CASE 3—T P J, male, aged 43, white, med No 27,438, admitted May 28, 1911 Diagnosis Pernicious anemia

June 16, 1911 Blood examination

Red blood cells, 1,544,000

Hemoglobin, 33 per cent

White blood cells, 3,200

Differential count

Lymphocytes	43 0%
Large mononuclears and transitionals	4 0%
Polymorphonuclear neutrophils	53 0%

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\*The infection occurred about one month after the present study of the blood was made

Nucleated reds were present in the proportion of 230 to 1,000 leukocytes. Poikilocytosis and anisocytosis were marked, some of the cells being unusually large. The evidences of regeneration of the red cells were striking.

CASE 4—H. M., male, aged 45, white, med. No. 27,336, was admitted May 4, 1911. Diagnosis: Aplastic pernicious anemia (autopsy).

May 4, 1911. Blood examination.

Red blood cells, 1,280,000

Hemoglobin, 20 per cent

White blood-cells, 1,200

Differential count of 100 cells

Lymphocytes	60.0%
Large mononuclears and transitionals	17.0%
Polymorphonuclear neutrophils	16.0%
Eosinophils	0.0%
Mastzellen	1.0%
Myelocytes, neutrophilic	3.0%
Unclassified	3.0%

Two megaloblasts and one normoblast were found. The blood showed a considerable degree of anisocytosis and poikilocytosis but the absence of many macrocytes and, indeed, of any very large ones was striking, the morphology of the cells suggesting a severe secondary rather than a primary pernicious anemia, except for the megaloblasts. Aside from the scanty nucleated reds, there were no signs of regeneration in the red cells. The occurrence of myelocytes and a few nucleated red corpuscles indicates a futile attempt at regeneration.

CASE 5—P. H., male, aged 56, white, med. No. 27,337, was admitted May 4, 1911. Diagnosis: Severe secondary (toxic) anemia (?), pernicious anemia (?). (The patient was employed in a dye factory and it is possible that the anemia was the result of his occupation, conclusive evidence is not yet at hand.)

June 7, 1911. Blood examination.

Red blood cells, 900,000

Hemoglobin, 15 per cent

White blood cells, 2,400

Differential count

Lymphocytes	37.0%
Large mononuclears and transitionals	3.0%
Polymorphonuclear neutrophils	57.4%
Eosinophils	2.0%
Mastzellen	0.0%
Myelocytes, neutrophilic	0.2%

No nucleated reds were found and there were no other evidences of regeneration of the red corpuscles. The absence of large cells is striking. Except for the lack of nucleated red cells and the presence of only slight poikilocytosis the blood bore a striking resemblance to that of Case 4. On vital staining with polychrome methylene blue, very few erythrocytes showed the reticulo-filamentous substance. After the red count had fallen to 530,000, defibrinated blood was given intravenously by Dr. W. L. Moss (who will include the case in a forthcoming report), and on June 13, 1911, an examination of the blood showed

Red blood-cells, 1,580,000

Hemoglobin, 19 per cent

White blood cells, 4,000

There was now a normoblastic crisis, 143 nucleated red cells per 1,000 whites. No megaloblasts were found and the intermediates were small.

1806 Locust Street, St. Louis — 406 Cathedral Street, Baltimore

# THE EFFECT OF SOME HYDROTHERAPEUTIC PROCEDURES ON THE BLOOD-FLOW IN THE ARM

A W HEWLETT, M D, J G VAN ZWALUWENBURG, M D,  
MARK MARSHALL, M D

ANN ARBOR, MICH

## INTRODUCTION

It is generally agreed that therapeutic baths exercise a profound effect on the circulation of the blood. The exact changes, however, are not fully understood and this lack of knowledge is due to a number of causes. In the first place it is not easy to transfer the results of animal experiments to man because the skin vessels in the latter are more active and the temperature regulation more exact. In the second place alterations in the distribution of blood in the body, seemingly the most marked circulatory effect of baths, are not readily studied in man. The blood-pressure gives no definite information as to this distribution because the dilatation of one set of vessels may be neutralized by the constriction of another set, and the changes in pulse tracings are extremely difficult to interpret.<sup>1</sup> On the other hand, the plethysmograph which records the volume changes in an extremity and presumably the variations in the contained blood has added greatly to our scientific knowledge of the action of hot and cold water on the distribution of blood. Its use, however, is limited because it is necessary to keep the individuals extremely quiet during manipulations.

Considering the difficulties encountered in trying to obtain exact data, it is not surprising that frequent contradictions occur in the hydrotherapeutic literature concerning the effects of baths on the peripheral circulation. For this reason it seemed important to approach the subject from a new direction. We have therefore studied the effect of some representative hydrotherapeutic procedures on the blood flow in the arm, using a method recently described.<sup>2</sup> Many of our results correspond with those already obtained by the plethysmograph, but they are of interest because they are expressed in terms of blood flow. As has been indicated, the use of the plethysmograph is limited, as the individual must remain quiet during the observations and because the instrument cannot be taken off and replaced during an experiment. For this reason the reaction after a cold bath and the effect of exercise and friction cannot be studied by the plethysmograph, and our ideas concerning these have been deduced

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\*From the Department of Internal Medicine University of Michigan

largely from such evidence as the sensations of the patient and the color and warmth of the skin. The method which we have used permitted a removal and a replacement of the instrument on the arm so that comparative records before and after treatments could be obtained. We have therefore been able to study the effect of exercise, friction and the reaction after cold baths.

#### EFFECTS OF LOCAL PROCEDURES

The application of hot or cold water to the arm is one of the simplest hydrotherapeutic procedures, and the effect of such applications on the local circulation has been studied by various methods. U. Mosso,<sup>3</sup> Sarah Amintin<sup>4</sup> and others have shown that in general the arm shrinks under the influence of cold and swells under the influence of heat. A. Mosso<sup>5</sup> has shown that the size of the volume pulse is diminished by local cold and increased by local heat, and Balli's<sup>6</sup> tachograms show similar changes. Lommel<sup>7</sup> has shown that the rate of propagation of the arterial wave is accelerated by local applications of cold. From these and other observations it has become generally accepted that the arteries and other blood-vessels in the extremities contract under the influence of local cold and dilate under the influence of local heat, and it has been assumed that the local blood-flow is lessened in the former condition and accelerated in the latter. Friedel Pick<sup>8</sup> has proved this for the legs of dogs by direct measurements of the venous outflow.

In order to study the effect of thermic stimuli on the local blood-flow, we have modified our method by partially filling the plethysmograph with water. The temperature of this latter could be varied by passing hot or cold water through an encased coil of block tin. Records of the blood-flow made at frequent intervals were compared with the temperatures of the water surrounding the arm.

It is well known that the volume of the arm often fluctuates considerably in the ordinary plethysmograph, and we found similar fluctuations in the rates of flow. Inaccuracies of the method undoubtedly accounted for many of the minor fluctuations. Others, however, were probably due to psychic or other nervous influences which, as Weber<sup>9</sup> and others have shown, exert a powerful influence on the caliber of the peripheral vessels. These nervous variations could usually be distinguished from those produced by thermic influences on account of their transient and variable character. They were most apt to be encountered when the blood-flow approximated the normal rate, and tended to diminish when the water surrounding the arm was either hot or cold. When both arms were studied, fluctuations were frequently encountered in the arm which was placed in an air plethysmograph and was not directly subjected to strong thermic stimuli. These observations are comparable to the experiments of Friedel Pick, who showed that when the leg of a dog was exposed to

hot or cold water the usual vasomotor effects of cutting or stimulating the sciatic nerve did not occur. The influence of strong thermic stimuli transcended the nervous influences.

The general qualitative effect of thermic influences on the local blood-flow in our experiments was very constant. Whenever definite results were obtained, heat always accelerated the local flow and cold always diminished it. A typical chart of this class of experiments is shown in Figure 1. It will be seen that the original rate of 3.7 c.c. of blood-flow per 100 c.c. of arm substance per minute when the arm was surrounded by water of 24°C was gradually reduced by the cooling of the water until a minimum rate of 1.1 c.c. was obtained when the water temperature had fallen to 14.5°C. In all of our experiments a similar fall occurred but we were unable to use very low temperatures on account of the pain in the arm caused by the cold. On this account, perhaps, we obtained no increased flows at very low temperatures such as would correspond to the

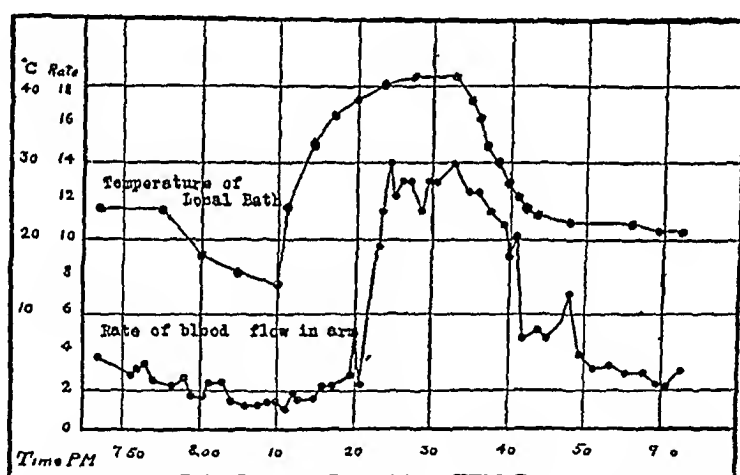


Fig 1—The effect on the local blood-flow of varying the temperature of the water surrounding the arm. Note that for corresponding temperatures the flow is more rapid when the temperature is falling than when it is rising.

swelling of the arm described by U. Mosso or to the relative increase of heat elimination described by Robinson and Stiles<sup>10</sup>. On this account also, perhaps, when the arm was again heated to a neutral temperature we obtained no excessive increases in the rate of flow such as one might expect from the changes in volume described by U. Mosso, or the changes in volume pulse pictured by A. Mosso. As a rule in our experiments the rate of flow did not immediately increase when the temperature surrounding the arm was raised, but remained relatively slower than it had been for corresponding temperatures when the temperature of the water bath was falling. Thus we obtained no records which could be interpreted as showing a "paralysis of the vessels" from cold.

High temperatures invariably produced a most marked acceleration of the rate of flow. This developed more suddenly in Figure 1 than in

most of our experiments, but there was nearly always a rapid increase in the rate of flow at about the time that the temperature of the water passed 35 to 38 C. The increases from the original rates to the maxima were always very marked, much more so than those which Friedel Pick obtained in dogs. The following figures give the rates per minute per 100 cc of arm substance before and after the application of heat: 3.7 cc to 14 cc, 4 cc to 29 cc, 6 cc to 22 cc, 5 cc to 26 cc, 3 cc to 26 cc, 4 cc to 22 cc, 6 cc to 45 cc.

When the temperature of the water bath was again reduced after reaching temperatures of 42 C to 50 C, the rate of flow always fell, but this fall never occurred promptly and for a given temperature of the arm bath the rate of flow was invariably faster than when the temperature was rising (Figs 1, 2 and 3). Similar results published by U. Mosso for the volume changes in the arm were interpreted as indicating a vascular paralysis, a subject which will be discussed later.

Several causes contribute to produce the fluctuations in the rate of blood flow which follow the local applications of hot or cold water. It is difficult, however, to estimate the exact part played by each. Theoretically one may consider (1) the direct action of heat or cold on the blood-vessels or their local nervous connections, (2) reflexes excited by thermic stimuli and acting on local vessels, (3) reflexes excited by thermic stimuli and acting on the vessels of the body in general, and (4) the effect of cooling or warming the blood. The separation of the first two of these or the local effects, from the last two or the general effects, can be accomplished by a simultaneous study of the two arms when only one of these is subjected to external changes in temperature.

Studies of this character have yielded very contradictory results. U. Mosso describes a single experiment in which the arm exposed to hot water became swollen while the opposite arm, exposed to an indifferent temperature, shrank. Sarah Amitin, in similar experiments, found that while the arm in hot water became swollen the opposite arm did not change volume. She found, however, that when one arm was exposed to cold water both shrank. Friedel Pick obtained unilateral effects in studying the action of thermic stimuli on the blood flow in the legs of dogs. On the other hand, many observers in recent years, notably O. Muller,<sup>11</sup> have emphasized the fact that the vessels in the two arms tend to act in unison when one is subjected to hot or cold applications. We have carried out several sets of experiments in which the rates of flow in the two arms were compared while one was exposed to hot or cold water and the other was in an air plethysmograph, and we are inclined to believe that the contradictory reports published by others may be explained by variations in the room temperature.



The first set of these experiments were made during the spring months of 1910, in a fairly warm room. During the application of heat to the arm, the body as a whole became warm and the individual perspired freely. Figure 2 shows the results obtained in one of the three experiments performed at this time, all with uniform results. It will be seen that the application of heat to the right arm caused an increased blood-flow in the left arm. In contrast with the right, however, this increase in the left took place somewhat later, did not reach the same high point and the rate decreased more promptly when the right arm was cooled to

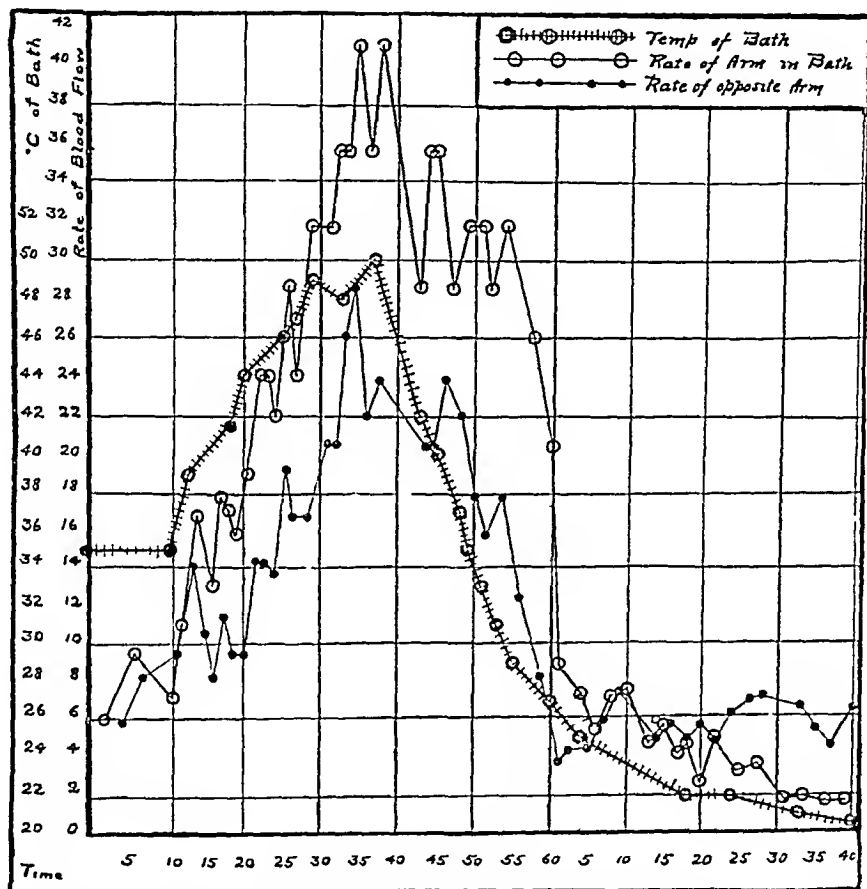


Fig 2—The effect of varying the temperature of the water surrounding one arm on the blood-flow in this and in the opposite arm, the room being warm. The right arm was exposed to the varying temperatures, the left was in an air plethysmograph. Note that when heat was applied the blood-flow in the latter rose later, did not reach the same high point, and fell more promptly. Also that when cold was applied the flow in the right arm fell below that in the left.

a neutral temperature. When the water was still further cooled (below 25°C), the rate in the arm exposed to the cold diminished, while it remained approximately normal in the other. The marked discrepancy between these results and those of U. Mosso and of Sarah Amitin led us to repeat this experiment in a cold room, taking care that the individual should remain slightly chilly throughout. In Figure 3 it will be seen that under these conditions the arm directly exposed to the changing

temperature showed the customary changes in blood-flow while the opposite arm showed throughout a slow rate of flow, the maximum increase not being over twice the original rate. When the water in the plethysmograph was cooled, both arms showed an extremely slow and approximately equal blood-flow. The different results in these two experiments show clearly that the room temperature exercises an important influence on the distant vascular reaction when hot or cold water is applied to a limited part of the periphery. They also show that the local effects of such applications are largely independent of the general effects. O Muller<sup>11</sup> also noticed that the temperature of the room disturbed the general effects, but in a somewhat different manner from what we have described. He states that when the temperature of the room was considerably below 20 C, the distant effects of cold were lessened and conversely when the temperature of the room exceeded 20 degrees the distant effects of local heat were lessened.

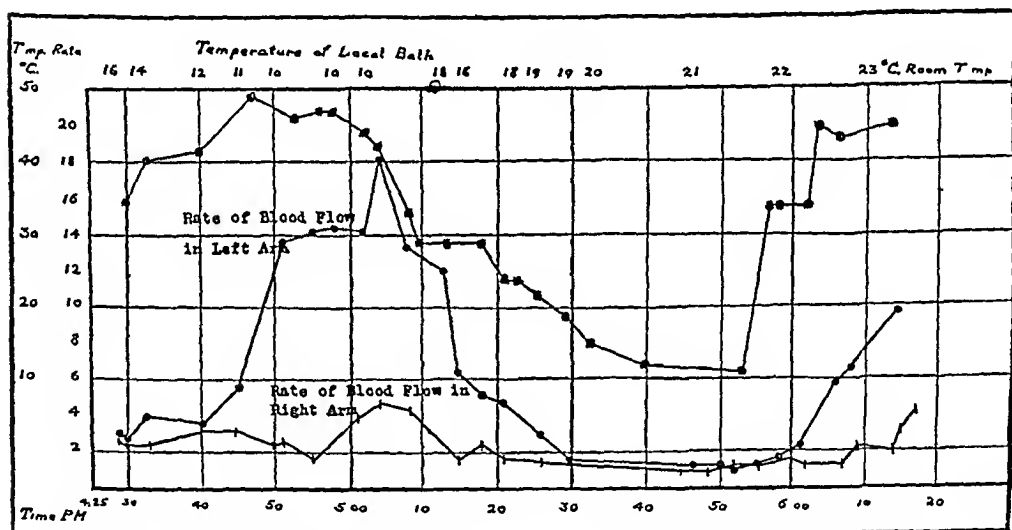


Fig 3—The effect of varying the temperature of the water surrounding one arm on the blood-flow in this and in the opposite arm, the room being chilly. The upper curve represents the temperature of the local bath, the middle the blood-flow in the arm to which the water of varying temperatures was applied, and the lower the blood-flow in the arm contained in the air plethysmograph. Note that heat increased the flow in the left arm very markedly while it did not greatly affect that in the right arm. At low temperatures both arms showed a very slow rate of blood-flow.

To demonstrate this more clearly a final experiment was performed, during which the room temperature and the temperature of the water about the arm were varied independently. During the first part of this experiment the room was kept at a constant temperature of 22 C to 24 C, while the temperature of the water bath surrounding the left arm was raised from 32 C to 41 C. The blood-flow in the left arm increased from an average of 5 cc per 100 cc of arm substance per minute, to

15 c c, while the blood-flow in the right arm varied but little from the original rate of 4 c c. During the second part of the experiment the temperature of the water bath was maintained at 42 C, while the temperature of the room was reduced from 24 C to 12 C. In this period the blood-flow in the left arm fluctuated in the neighborhood of 16 c c while the blood-flow in the right arm fell from the neighborhood of 4 c c to about 2 c c. During the third period the temperature of the water surrounding the left arm continued to be about 42 C while the temperature of the room was raised from 12 C to 30 C. In this period the rate of blood-flow in both arms increased. That of the left rose from 17 c c to 27 c c, that of the right from 2 c c to 7 c c. During the fourth period the room was kept warm and the temperature of the water surrounding the left arm was reduced from 42 C to 14 C. The rate of blood-flow in the left arm fell from 27 c c to 2 c c, while that in the right arm fell from 7 c c to 4 c c. In the final period the temperature of the room was again reduced to the chilling point and the rates in both arms fell still further, approximating each other at a little over 1 c c. In this experiment the blood-flows in the arm exposed to the changing temperatures of the water followed these changes rather closely and were but moderately affected by the room temperature. The blood-flows in the opposite arm, on the other hand, depended chiefly on the room temperatures but was moderately affected by the changes in the temperature of the water surrounding the first arm.

Our experiments demonstrate that thermic stimuli produce both local and general effects on the peripheral blood-vessels. The former are shown by the facts that (1) when heat is applied the blood-flow is always relatively faster in the arm to which it is applied, (2) when the individual is kept cool or chilly, the rate in the opposite arm may not be accelerated, and (3) when cold is applied the blood-flow in the affected arm is often less than in the opposite arm. The effect of local applications on the blood-vessels of the opposite arm is indicated by the fact that the blood-flow in the latter frequently undergoes changes similar to, though usually not so great as, those which occur in the arm directly treated.

The factors causing the distant effects of heat and cold will be discussed later. Concerning their local action we have two possibilities. The first of these would attribute these effects to reflexes originating from the heated or cooled skin and acting on the local vessels. While it is possible that such reflexes occur, they do not seem to be necessary, for Friedel Pick observed characteristic changes in the blood-flow following thermic applications to the legs of dogs even after the sciatic nerves were cut. This seemed to indicate that thermic influences may act directly on the local nervous or vascular apparatus. Similar results have been obtained by others.<sup>1</sup>

When the arm is heated excessively, signs may appear which indicate a loss of contractile power on the part of the vessels. U. Mosso assumed the existence of such a "vascular paralysis" as the result of heating the arm, and based his assumption partly on the observation that after a thorough heating the vessels do not contract promptly when cold is applied. While our observations on the blood-flow confirm his, we are inclined to give them a different interpretation. The temperature to which the tissues are exposed is not the same as the temperature of the surrounding water bath. When the tissues are thoroughly heated the local blood-flow is markedly increased, the deep layers of the skin are relatively protected from the cold water bath, and one would not expect a sudden contraction following its use. Occasionally, however, the skin remains red for hours, even days, after exposures to very hot water. Furthermore, in several of our experiments the curves obtained after very hot water were peculiar in that only a small amount of blood could enter the arm at a uniform rate. To our minds this indicated that the vascular reservoir was diminished, and taken in conjunction with the fact that the rate was very fast and the arm red, it seemed to us probable that the vessels were dilated to their utmost and did not empty sufficiently between determinations to allow the reception of much more blood. This effect persisted for some time after the rate began to fall as a result of cold applications but ultimately completely disappeared. In such a case, and also where the skin remains abnormally red, one might speak of a "vascular paralysis."

#### EFFECT OF GENERAL PROCEDURES

General hydrotherapeutic treatments are usually initiated by a hot procedure, such as an electric cabinet bath, and are usually terminated by a cold procedure, such as a cold shower. In some cases cold procedures alone are used. Exercise, friction, the mechanical action of douches, and the temperature of the room are important accessories. In the present study we have aimed to determine the effect of general hot and cold procedures on the circulation in the arm. We have also tried to outline the part played by some of the above named accessories. Finally, mouth temperatures have been taken during many of the experiments for the purpose of comparing these with the peripheral blood-flows and with the ability of the individuals to react. Prolonged cold and medicated baths such as are used in the treatment of fever and of heart disease were not studied.

#### SUMMARY OF EXPERIMENTS

A number of experiments were carried out, the results of which are shown below in the form of tables. A general discussion follows. Many details of the experiments have necessarily been omitted from the tables.

such as, for example, the fluctuations in blood-flow caused by nervous influences or by errors in the method employed. Some idea as to the extent of these fluctuations may be obtained from Figures 1 to 4. When the fluctuations were very marked the figures given in the tables have been starred. When more or less continuous changes in rates occurred, especially after hot or cold procedures, the changes have been indicated by a dash connecting the earlier with the later rates. All temperatures have been expressed in the centigrade scale, and the blood-flows have been expressed in terms of the number of centimeters of blood entering 100 c c of arm substance per minute. The plethysmograph always included the hand, forearm and lower arm.

In the first set of experiments, represented in Table 1, the individuals were placed at rest in a bath tub, and the original rates were taken while the individuals were covered by a light blanket. Hot water (41 C to 45 C) was then run into the tub. This usually covered the lower extremities, the abdomen and parts of the chest and of one arm, leaving the arm in the plethysmograph outside of the water. The subjects were left in the hot water until a profuse perspiration occurred. After this the water was allowed to run out of the tub and a spray with tap water under high pressure and at a temperature of about 15 C was given without moving the individual or the apparatus. The rates of flow through the arm were taken at frequent intervals throughout the experiments. In some instances the shower was repeated once or twice, but the results of these secondary showers are not charted in this table.

TABLE 1—HOT TUB BATHS FOLLOWED BY COLD SPRAYS

Name	Room Temp	Original Rate	Average Maximum Rate in Bath	Rate when Water Ran Out	After Spray	Maximum Mouth Temp in Bath
Hew	25 C	3.3*	14.4	14.4	14.5	38.5 C
Hew	23 C		20.0	16.0	14	38.4 C
Meg	25½ C	2.2	12.4	7.1	3.2	37.9 C
Alex		4.3*	20.0	13.0	5.4	37.9 C
Sti	24 C	2.7	18.0	14	4.3	
Gan	22 C	2.2	22.0	10	2.5	
Sch	21 C	2.0	13.0	6.5	4.0	38.3 C
Cha	21 C	2.0	14	2.2	2.0	38.1 C
Lot	23 C	2.0	11.0	10.1	3.6	

In the experiments shown in Table 2 the same procedures were used except that in place of hot water the individual was surrounded by numerous blankets which were heated by an enclosed set of incandescent lamps. The direct rays from the lights did not reach the skin. The "after spray" rates were taken as in the previous set of experiments. The individual then took an ordinary cold shower, dried himself and dressed. The rates after these procedures are given in the last column.

TABLE 2—HOT AIR BATHS FOLLOWED BY COLD SPRAYS

Name	Room Temp	Original Rates	Average Maximum Rates	Rates when Blankets were Re-moved	After Spray	Highest Mouth Temp	After Ordinary Shower
Hew	21 C	65	100	60	50	37.2 C	74
Hew	26 C	57	12	100	43	37.5 C	42

In Table 3 the individuals were placed at rest in a tub, and the shower was given without any preliminary heating

TABLE 3—COLD SPRAYS WITHOUT HOT PROCEDURES

Name	Room Temp	Rates Before Shower	Rates After Shower	Rates After Dressing
Lot	23 C	14	13	18
Lil	23.5 C	26	13	25

Two objections may be raised to the results obtained in these experiments. In the first place the arms from which the observations were taken were kept continuously in the air plethysmograph and did not come in contact with the hot or cold water. In the second place important accessories to a therapeutic treatment were absent, such as the exercise taken during or after the bath and the local friction from douches and from rubbing with hands or towels.

Table 4 shows the results obtained during observations made on patients of the psychopathic hospital who were taking baths for therapeutic purposes. We were permitted to make these observations through the courtesy of Dr. A. M. Barrett. In these cases rates were taken before the electric cabinet bath, after the electric cabinet bath, and finally after cold procedures which consisted of gradually cooled showers and douches.

TABLE 4—ELECTRIC CABINET BATHS FOLLOWED BY COLD SHOWERS

Name	Average Room Temperature	Original Rates	After Coming Out of E. C. B.	After Cold Procedures	Highest Mouth Temperatures
Sm1	26 C	67	100	85	37.5 C
Schu	24 C	47	115	45	37.7 C
Wood	24 C	53	100.6	52	37.3 C
Per	24 C	50*	110	52*	37.5 C

In Table 5 are recorded the effect of cold showers as ordinarily taken by vigorous young adults. The rates were taken before undressing, after undressing and finally directly after drying, the individual being lightly covered with a blanket.

TABLE 5—COLD SHOWERS

Name	Room Temperature	Dressed	Undressed	After Shower	Mouth Temperatures Before	After
Hew	25 C	62	67	44-58	37.0 C	36.6 C
War	25 C	20	24	59	36.7 C	37.2 C
Hoy	25 C	26	38*	41	37.0 C	36.9 C

In these last two sets of observations the apparatus was taken off and applied several times. The cold procedures were accompanied by considerable exercise and were followed by a vigorous rubbing with a towel. While it was impossible to obtain as many records in these cases, and while the immediate effects of procedures could not be followed, yet they represent more accurately the changes which occur in practical bath treatments.

#### EFFECT OF HOT PROCEDURES

As hot procedures, the full tub bath, the hot air bath and the electric cabinet bath were used and these were continued until the individuals perspired profusely. During these applications of heat the mouth temperatures invariably rose. During the hot air and the electric cabinet baths, the mouth temperatures rose to at least  $37.2^{\circ}\text{C}$ , and usually to  $37.5^{\circ}\text{C}$  or  $37.7^{\circ}\text{C}$ . In the full tub baths the individuals were partly covered with hot water ( $41^{\circ}\text{C}$  to  $43^{\circ}\text{C}$ ), and the body temperatures usually rose above  $37.8^{\circ}\text{C}$  and frequently above  $38^{\circ}\text{C}$ . During these hot procedures the rate of blood-flow through the arm invariably increased, never being below 10 c c per 100 c c of arm substance per minute, and often exceeding 20 c c. These rates were from two to ten times the original rates, but this ratio seemed to depend more on the original than on the final rate. The flow increased, even though the arm itself was not directly exposed to high temperatures. While in general the acceleration of flow was greater when the mouth temperature was high, there seemed to be no strict parallelism between the two.

When the hot procedures were over and the individuals were exposed to ordinary room temperatures, a fall occurred in the rate of blood-flow through the arm, usually reaching 70 per cent or less of the highest previous rate. In one patient (Table 1 Cha), who was quite unaccustomed to baths, the rate rose during the hot tub bath from 2 c c per 100 c c of arm substance per minute to 14 c c, but it fell to the original rate when the hot water was let out of the tub. The body temperature at this time was  $37.8^{\circ}\text{C}$ , and we regarded this abrupt fall as pathological. The results obtained on the patients of the psychopathic hospital (Table 4) showed rather less than the customary accelerations of blood-flow after the electric cabinet bath. Two causes contributed to produce this result. One was the initial warm temperature of the room, which gave these patients relatively rapid rates before entering the cabinet. The other was the fact that our apparatus was reapplied after the patients had come out of the cabinet, and that during the elapsed time the rates probably fell below what they had been in the cabinet.

#### EFFECT OF COLD PROCEDURES

The effect of simple cold procedures following the hot procedures was quite uniform in that they always caused a fall in the rate of flow through the arm. The extent of this fall varied greatly. In some the cold reduced

the flow to less than the original rate while in others the reduction was much less marked, and the flow was left considerably above the original, though usually below that produced by heat. In a general way, when no exercise was taken and no friction was given, the rate of blood-flow was more apt to remain above the original rate if the body temperature had been much elevated by the preceding heat. In such cases the individuals usually took the cold showers with ease and were left warm and exhilarated, reactions being obtained without exercise or friction.

When primary cold procedures were given without exercise and without friction, or when repeated cold procedures without these were given after hot ones, the rate of flow through the arm was reduced by each shower. This result was obtained both when the arm studied had been directly exposed to the cold water and when it had been protected by being enclosed in the plethysmograph.

Attempts were made repeatedly to obtain records during the cold showers but the results were rather unsatisfactory, partly on account of involuntary movements of the individual and partly because it was difficult to protect the plethysmograph from the cold spray which caused the enclosed air to shrink. We frequently gained the impression, however, that the flow during the shower was somewhat slower than it was a few minutes later.

#### EFFECT OF VARIATIONS IN BODY TEMPERATURE

Warm procedures invariably raised the mouth temperatures to some extent. In our experiments this was most marked in those taking hot water tub baths which usually raised the temperature to  $37.9^{\circ}\text{C}$  or over. When hot air or electric cabinet baths were used, the rises in temperature were less marked but the mouth records often exceeded  $37.5^{\circ}\text{C}$ . The more marked effect of hot water baths is due in part to the high specific heat of water but still more to the fact that they prevented evaporation from the portions of the body immersed in water so that the individuals lost this method of maintaining their normal temperatures. During cold procedures the body temperatures were not reduced below the normal in a large number of therapeutic treatments studied, but when cold procedures were given without following the customary rules of hydrotherapy, it frequently happened that the mouth temperatures fell below  $36.7^{\circ}\text{C}$ .

To what extent do these variations in the body temperature influence the blood-flow in the arm and the various phenomena accompanying hydrotherapeutic treatments? The effect of the body temperature is naturally a general one and not dependent on the point at which the thermic application is made. It must, therefore, be distinguished from the local effect of hot or cold water which usually exceeds the distant effects. It would seem from experimental evidence that such distant effects of hot procedures may be produced either by reflexes excited by



stimulation of the thermic sense organs in the skin<sup>12, 13</sup> or by changes in the temperature of the carotid blood which supplies the brain<sup>14</sup>. The relative importance of these factors in producing the circulatory changes of man during the therapeutic use of water has not been carefully studied by scientific methods, though recent writers<sup>11</sup> have usually assumed that distant effects are caused by reflexes arising from the cutaneous thermic sense organs and acting on the peripheral vessels by way of the vasomotor center.

Several facts indicate that the body temperature is a factor which cannot be neglected in this connection. The ordinary measures used in therapeutic institutes for hydrotherapy emphasize the importance of preventing heat losses from the body. The rooms are kept unusually

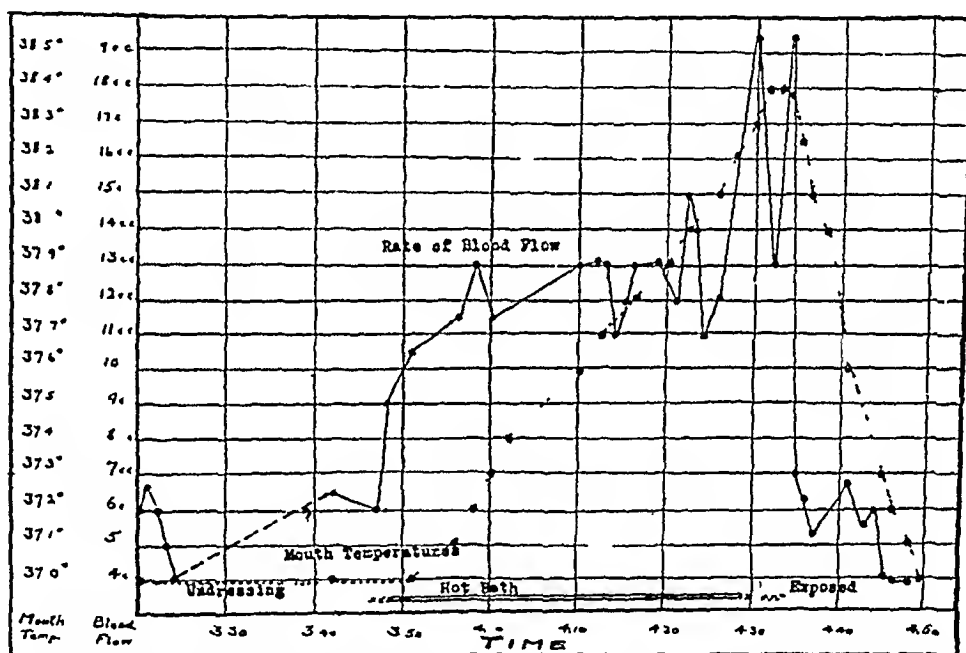


Fig. 4—The relation between the mouth temperature and the blood-flow in the arm during a hot tub bath. Note that the rate rose at the beginning of the bath before the mouth temperature showed a change, also that the rate fell when the water ran out while the mouth temperature was still above 38°C.

warm, the cold procedures are short, and individuals not accustomed to baths are given preliminary hot procedures. In our experience when the body temperature is reduced, cold procedures are apt to leave the individuals chilly and with a slow peripheral rate of flow. After hot water baths, on the other hand, where the body temperature is considerably elevated, cold procedures are borne unusually well, even though the room is cold. The one exception to this rule which we observed (Cha, Table 1) was regarded as a pathological chilling on exposure to a cool room after a warm procedure.

In order to study more accurately the relation between the effect of thermic stimuli and the effect of body temperatures, two experiments

were performed in which an effort was made to distinguish these factors. The experiments were performed in a cool room ( $18.5^{\circ}\text{C}$ ), the individuals were given hot tub baths, and the body temperatures were raised to about  $38.4^{\circ}\text{C}$ . The water was then run out of the tub and the individuals left exposed to the cool air of the room until the mouth temperatures fell to normal. A series of readings were made of the mouth temperatures and of the rates of flow through the arm. Essentially the same results were found in both experiments but the more striking of the two are shown in Figure 4.

In Figure 4 it will be seen that the original rate of about 6 c.c. fell under the influence of a cool room and partial exposure to 4 c.c. The individual then undressed and was covered with a light blanket, the rate at the end of this being 6.5 c.c. The tub was filled with water of a temperature of  $41.7^{\circ}\text{C}$ , and the rate of blood-flow rose almost immediately to above 10 c.c. This change occurred before any rise in the mouth temperature was recorded. As the body temperature rose, the rate of blood-flow took a slightly higher level and finally with the body temperature of  $38^{\circ}\text{C}$  the blood-flow reached a high mark of 19 c.c. In the other experiment this secondary rise of blood-flow did not occur. When the water was run out of the tub and the individual was exposed to the cold air of the room, the rate of blood-flow fell almost immediately to the neighborhood of 6 c.c., although at this time the mouth temperature remained above  $38^{\circ}\text{C}$ . A marked fall in blood-flow did not occur until the temperature reached  $37.3^{\circ}\text{C}$ , when the rate fell somewhat below the original rate.

In these experiments we have a clear demonstration that the rate of blood-flow in the arm which was kept continuously in the air plethysmograph varied independently of the body temperature. The rate increased promptly when the body was covered with hot water and before the body temperature was raised and it fell promptly when the water was let out, although the body temperature remained high. We believe, however, that the experiments also showed a definite effect of the elevation of body temperature. From our experience, naked exposures to a room temperature of  $18.5^{\circ}\text{C}$  should send down the rate much more than what was found seven minutes after the hot bath<sup>15</sup>. It seems probable that the elevated body temperature prevented a still further fall of blood-flow. In contrast to these observations we have noted on several occasions that when the body temperature was slightly subnormal, exposure to a cool room almost immediately reduced the flow to the neighborhood of 1 c.c., and the individual became very chilly. We believe that these experiments indicate that while the external temperature exercises a more powerful effect on the peripheral blood-flow than does the body temperature, the effect of the latter should not be neglected. In practical hydrotherapy the

slight elevations of temperature caused by the hot procedures, and the avoidance of excessive heat losses tend to prevent the excessive constriction of the vessels with chilling which are apt to follow exposure to cold air or cold water if the body temperature is normal or subnormal

#### THE EFFECT OF EXERCISE AND FRICTION

We have already stated that in our experiments, cold procedures without exercise or friction were invariably accompanied by a fall in the rate of flow through the periphery (Tables 1, 2 and 3) This occurred even though the spray did not last long and even though the subjects felt exhilarated and not chilly Similar results were obtained when the arm was taken out of the plethysmograph and directly exposed to the spray

In Table 5, however, it will be seen that in two of three individuals a primary cold bath was followed by an acceleration in the peripheral rate of flow Similar results were obtained on several occasions at the end of long tub experiments when the individual took a final cold shower with exercise and rubbing (See for example the first experiment in Table 2) It would appear from a comparison of our results that when an acceleration of flow occurs after primary cold procedures, it is due to the exercise and friction with which these are accompanied This was especially noticeable in Table 5, Wai, who showed the most marked increase of flow, was unaccustomed to showers, took a very short one, and exercised vigorously The difference in our results may have been due in part to the fact that where the arm was kept continuously in the plethysmograph careful drying was not attempted and the rate was held down by the wet condition of the skin Under any circumstances, it is certain that primary cold procedures never accelerate the rate of flow through the arm to the same extent as do hot procedures In some cases a moderate acceleration is obtained, in others the rate is not much changed When, however, the cold is given without friction, exercise and drying, the rate of flow invariably falls as a result of the procedure

#### THE REACTION

The reaction after cold procedures plays an extremely important part in practical hydrotherapy The patient is said to react well when he feels exhilarated and warm and when the skin becomes pink The absence of these — but especially the sense of chilliness — constitutes a failure to react It is not always easy to define a reaction This is especially true when the individual feels exhilarated and warm immediately after the cold procedure but becomes chilly on the least exposure or spontaneously within the next half hour or so The conditions which are used to favor reaction are preliminary hot treatments, warm rooms, short cold procedures, and the use of exercise and friction

In our experience, decided failures to react are always associated with a slow peripheral rate of flow. This was seen especially in those experiments where successive sprays were given to individuals who had been heated by a hot tub bath. In these cases the chilliness indicative of the failure to react always occurred when the blood-flow in the arm had become unusually slow. On the other hand, even a fairly typical reaction was not necessarily accompanied by a fast rate of blood-flow through the arm. In some cases (Table 2) the rate fell after a cold spray and yet the individuals gave the appearance and had the sensations of fair reactions. In such cases the red color of the skin must have been a purely local phenomenon and not associated with a dilatation of the deeper vessels. Usually the best reactions were seen when the rate of blood-flow did not sink much below the original rate, and quite frequently it was moderately elevated during the reaction. Our experiments seem to dispose finally of the old views of Winternitz which have been subjected to a destructive criticism by Matthes,<sup>1</sup> concerning the effect of cold and heat on the blood-flow in the arm. Winternitz believed that heat caused a "passive" dilatation of the vessels with slowing of the blood-current. Numerous physiological experiments as well as our observations on man have shown that heat markedly accelerates the rate of blood-flow in an extremity. The effect of cold, however, is more complicated. It is well recognized that under ordinary conditions cold contracts the blood-vessels and lessens the blood-flow. When intense cold is applied for some time, as in the case of an ice-bag, it causes a redness due to a dilatation of the local capillaries. We are unable to say whether this is accompanied by an increased flow or not. Furthermore, in the reaction after cold procedures it has been assumed that there is dilatation of the blood-vessels, and Winternitz went so far as to state that this "active" dilatation, in contradistinction to the dilatation caused by heat, is accompanied by an increased flow. Our experiments indicate that while the blood-flow may be increased during reaction this is never very marked and it is never increased to the same extent as it is during hot procedures.

On the other hand, we frequently obtained the impression that a secondary dilatation of the blood-vessels may occur following cold procedures independently of the immediate effect of exercise and friction, though it was difficult to be certain that this dilatation did not result merely from the cessation of the cold stimulus. In one case (Table 5, Hew ), however, we had an unusually clear association between the glow of a reaction and an increase in the rate of blood-flow. In this experiment the original rates of flow varied from 5.5 c.c. to 7.2 c.c. Immediately after undressing a rate of 6.7 c.c. was obtained, but a cold draft from the room in which the cold shower was running caused a momentary chilliness with reduction of the rate to 4 c.c. An ordinary cold shower was then

taken, following which the individual dried himself, returned to the tub, and was loosely covered with a dry blanket. The rates of flow taken immediately after were 48 cc and 42 cc, and at this time he still felt a little cold from the water. After the second determination a feeling of warmth was experienced, and with this the rate of flow increased to 56 cc and 6 cc. In this case the feeling of warmth and the increased rates were not due to the immediate effect of exercise or friction because they occurred when the individual was at rest. This glow with normal or somewhat increased rate of flow may occur even though the body temperature is subnormal. We were able to demonstrate this repeatedly when cold showers with exercise and friction were taken at the end of long tub exposures. While it is possible thus to raise the rate by the ordinary cold shower in vigorous individuals with subnormal temperatures, and while at the time these individuals often feel momentarily exhilarated and warm, it was noticed repeatedly that they were at the same time very sensitive to chilling influences and that a slight draft would cause a chilling sensation with a marked slowing of the rate. It was also noticed that when these individuals remained quiet in a room of ordinary temperature the glow was apt to be followed by chilliness. It seemed to us therefore that while a momentary reaction may be produced when the body temperature is subnormal, such a reaction is apt to be fleeting and followed by chilliness on slight exposure.

Our experiments support the general practice in hydrotherapeutic rooms of preventing such heat losses that the body temperature is lowered. Even when this is done, some individuals (Table 1, Cha.) may chill when exposed to cold air or cold water. The ideal conditions for a reaction after cold are attained when exercise and friction are used, the room is warm, and the body temperature is not allowed to fall below the normal.

#### CONCLUSIONS

- 1 When hot water is applied to the arm, the local rate may be increased from four to eight times, and when cold is applied the local rate may fall to one-half or one-fourth of the original.

- 2 These variations are often associated with similar, though less-marked changes in the blood-flow in the opposite arm. The latter is also influenced by the room temperature and the chilliness or warmth of the individual.

- 3 A diminution of the contractile power of the vessels may occur after exposure to excessively hot water.

- 4 General hot procedures cause a marked acceleration in the blood-flow through the arm, and general cold procedures without exercise, friction or drying decrease the blood-flow in the arm.

5 When exercise, friction and drying are given with cold procedures, the slowing may be more or less neutralized and the rate may even be raised somewhat above the original

6 Acceleration of blood-flow in an arm not directly exposed to the hot procedure is due in the main to reflexes excited by thermic stimulation of the cutaneous sense organs. The rise of body temperature, however, tends to prevent an excessive contraction of the peripheral vessels when the individual is exposed to cold

7 If the body temperature is subnormal an immediate reaction may follow cold procedures which are accompanied by friction and exercise, but the individual is liable to become chilly later

8 Reactions are usually, but not necessarily, accompanied by normal or moderately increased rates of flow

902 Baldwin Avenue

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# AN INVESTIGATION OF THE DEPRESSOR ACTION OF PITUITARY EXTRACTS<sup>1</sup>

CAREY P. McCORD, M.D.

ANN ARBOR, MICH.

## I. INTRODUCTION

It is generally conceded that intravenous injections of the extract of the infundibular portion of the pituitary gland cause a rise in blood-pressure, that this rise is due to a peripheral constriction of blood-vessels, and that when repeated injections are made, the rise in pressure diminishes with each injection until a fall in pressure occurs. This change in the effect of repeatedly administered injections of pituitary extracts is designated as its "depressor action." No attempt will be made here to cover with detailed references the previous work on this subject, which is readily accessible in a recent article by Wiggers.<sup>1</sup>

A brief summary of the commonly accepted interpretation of these results seems, however, necessary. In 1899 Schafer and Vincent<sup>2</sup> suggested that extracts of the pituitary gland contained two substances, one having a pressor, the other a depressor effect, the former inducing a constriction of arterioles, the latter a dilatation. After repeated injections of the extract of pituitary gland, the pressor substance lost and the depressor retained its influence on the blood-vessels, so that the rise in pressure was gradually replaced by a fall. A perusal of the work of Schafer and his co-workers emphasizes the fact, however, that this must be regarded as a plausible explanation rather than, as is commonly assumed, a demonstrated fact, for they not only failed to isolate these substances chemically,<sup>3</sup> but they have not excluded the following possibilities of error, namely, (1) the decreased cardiac output may be accountable for the fall of blood-pressure, (2) an increased central dilator action develops, overpowering the peripheral constriction, (3) lack of proof that the peripheral vessels dilated when the fall of pressure occurs, (4) repeated injections can convert the constriction of peripheral origin into a dilation.

The scope of this research was limited to the solution of some of these undetermined problems by more direct experimental methods, and

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\*From the Research Laboratories of Parke, Davis and Company, Detroit

<sup>1</sup> Wiggers Jour Med Sc, 1911, cxli, No 4, p 502

<sup>2</sup> Schafer and Vincent Jour Phys, 1899, xxiv, 19, Jour Phys, 1900, xlv, 87

<sup>3</sup> Schafer and Herring Phil Tr, Roy Soc London, series B, 1908, cxix, 1

other facts regarding this drug's action were touched on only as necessity demanded. By this means, it was hoped to throw additional light on the nature of the depressor action of pituitary extracts.

## II MATERIAL AND METHODS USED

The infundibular portion of the gland was ground up and dried without any preservative. A solution of this material in Locke's solution was made of such strength, that each c c of the solution equaled 0.1 gm of fresh gland. This was then heated on a steam bath, so as to precipitate partly the protein material, which was later separated by filtering. The solution had a specific gravity of 1.010. This preparation deteriorated on standing. When the solution was sterilized, it kept permanently. This preparation which was made each day was used as a standard of all the work, and is the one referred to throughout the paper unless special designation is made. At times, however, a solution made in the same way, but of greater strength, was used. Pituitrin, the preparation which has been described by Aldrich, was also employed.<sup>4</sup>

For these experiments both dogs and rabbits were used, but principally the former. The anesthetic was uniformly chlorotone (0.3 gm per kilo of body weight) in oil, injected intraperitoneally. In dogs a subcutaneous injection of morphin preceded the administration of chlorotone. The external jugular vein was exposed for injections. The blood-pressure was recorded through the carotid artery, by means of mercury or Huithle's manometers. The contractions of the dog's heart were recorded by means of the cardiac oncometer. The cardiograph was used in case of the rabbit. In all experiments on dogs the breathing was natural. After the insertion of the oncometer the chest was sewed up, stitches being taken through the cut intercostals, through the muscles of the chest and through the skin. The site of the incision was covered with a mixture of petrolatum and wax, which rendered the thorax airtight. The respirations were recorded by the transmission of the changes in intrathoracic pressure through a thoracic cannula. During the period in which the chest was open, artificial respiration was given in the manner common to laboratories.

## III THE EFFECT OF BLOOD-PRESSURE

The blood-pressure phenomena arising from the intravenous injection of extracts of the pituitary gland into anesthetized animals are in no wise peculiar to this particular work, but correspond to the results reported generally. The results from the initial injection, allowing for normal variations, are constant and the tracings typical. Within a few seconds of the injection, the blood-pressure rises abruptly and

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<sup>4</sup> Aldrich. *Am Jour Phys, Proc Soc*, 1908, *xxi*, 23



sharply, the cardiac oscillation increases in size, and the heart-rate is slowed. A tracing presenting these results may be designated as a "typical pituitary curve." However, a number of variations are observed such as instances (1) in which no slowing up occurs, (2) in which, as the summit of the pressure height is neared, a slight and often imperceptible fall in pressure takes place (this fall in pressure is very transient, and the increase in pressure is soon resumed and generally reaches a point above that prior to the fall), or (3) in which, after a gradual fall a second slight increase in pressure occurs (Fig 1). The second and third variations occur very frequently in rabbits but only to a limited extent in dogs.

The rise of pressure persists for a considerable time, but generally approaches normal again within ten minutes, and only in exceptional cases remains above normal for a period of twenty minutes. The first "repeat dose" in dogs is not inactive, as has been shown by Schafer, for other animals. In none of these experiments did a second injection fail to produce a sharp rise in pressure. In rabbits, however, a large number of second injections were ineffective or caused a fall in pressure. In dogs the rise following the second injection is much more gradual, and the extent and duration of the rise is not so pronounced as after the first injection. This progressive lessening and lagging in the rise in pressure may be obtained for four or five injections, after which time the substance fails to act or else causes a depressor effect (Fig 2).

All further experiments were instituted in an attempt to explain these blood-pressure variations.

#### IV ACTION ON THE BLOOD-VESSELS

*Peripheral Action*—Since the rise in pressure is mainly attributed to a peripheral action on the blood-vessels, an insight into the exact nature and extent of this action was attempted by the perfusion method. The individual organs were isolated and perfused with a regularly interrupted stream of Locke's solution under constant pressure, and heated by passage through a condensing tube. The outflow was constantly recorded, together with the oscillation of the perfusion pressure. The preparation of pituitary extract, already described, was slowly injected into the circulating medium with a hypodermic syringe.

*Kidney*—Ninety-five injections were made. Of these, eighty-five gave an initial constriction of the blood-vessels, while ten injections were followed by a dilation. In sixty-five a single vaso-constriction with a quick return to normal occurred. In the remaining thirty a secondary action of various kinds was observed. Five injections gave a constriction of the blood-vessels followed by a subsequent dilatation, five injections constricted the renal vessels permanently, ten of the injections causing

a primary constriction of the blood-vessels were followed by a secondary constriction; of the injections producing an initial dilatation, seven showed a secondary constriction. In ninety-two of the total ninety-five experiments (97 per cent) a constriction took place, and in only three (3 per cent) was there a pure dilatation.

Repeated injections gave no evidence of fatigue on the part of the vessels. As high as twenty injections were made on a single kidney, and the response to the drug was as prompt in the last as in the first. After the fifth or sixth injection, the amount of constriction was no longer constant owing to the edema of the organ. Up to this point, however, injections of equal quantities of pituitary extract gave the same amount of constriction (within 2 per cent). Since this is true, it is possible that herein lies a reliable method for the standardization of the preparations of this drug. When a series of injections were made with doses ranging from 0.3 c.c. up to 2 c.c., the amount of constriction was not proportional to the amount of the substance injected. For example, the constriction that followed an injection of 2 c.c. was not double that which followed an injection of 1 c.c.

*Spleen*—The numerous collateral vessels to this organ were tied off. The capsule was not removed as in the case of the kidneys. A series of ten spleens were perfused. Following an introduction of 2 c.c. of pituitary extract the splenic vessels showed a constriction with an average decrease in outflow up to 60 per cent and a duration of the constriction of about two minutes.

*Liver*—The livers of guinea-pigs were perfused through the portal vein. Pituitary extract caused a constriction of the hepatic vessels which was not so marked as was obtained with renal vessels but which persisted for a greater length of time.

*Coronary Vessels*—For perfusing the heart, Ringer's solution was used. The cannula was placed in the descending branch of the left coronary artery, the heart being in standstill. The transverse branch of the left coronary artery and the right coronary were tied off. When dogs' hearts were perfused by this method, the injection of the pituitary extract was always followed by a constriction of the coronary vessels. Coronary vessels which responded readily to both adrenalin and pituitrin were injected with ergotoxin, which paralyzes the nerve endings or myoneural junctions. Subsequent injections with adrenalin elicited no constriction, and in some cases even a dilatation occurred, while the constrictor action of the pituitrin was even more pronounced than before the injection of ergotoxin. It would appear that adrenalin and pituitary extract have not a common point of action, and that the muscle fiber itself is the point of action for the latter.

*Lungs*—Solitary lobes of the lung of guinea-pigs were perfused. The lobe was inflated through the bronchus and tied off, so that the inflation was maintained throughout the experiment. Unless this was resorted to, the changes in the vessel wall were not apparent, since the air spaces would permit alterations to take place in the vessels which would not affect the recording apparatus. After this precaution had been taken, it could be seen that the injection of pituitary extract produced a constriction of the blood-vessels.

*Embryonic Vessels*—The bodies of unborn pups were perfused through the thoracic aorta. The thoracic veins were cut to allow an easy outflow for the perfusing fluid. Both adrenalin and pituitin were

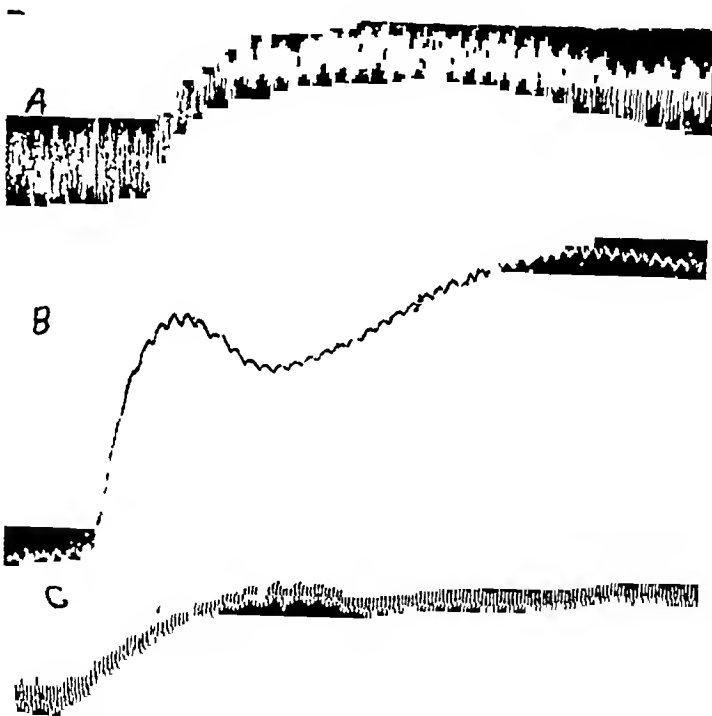


Fig. 1—A, blood-pressure tracing showing typical effect of pituitary extract; B and C, variation types.

injected, and the response from each consisted in a marked constriction of the blood-vessels.

*Limbs*—In one experiment the lower limb of a living and intact animal was perfused through the femoral artery. The sciatic nerve was dissected and the thigh, exclusive of this nerve, was tied off with a bandage from the other parts of the body. A constriction, such as had been seen in the other experiments, took place here on the injection of pituitin.

*Summary*—These experiments show that the pituitary extract acts on all the vessels of the body, and that the action is similar in quality for all parts of the body, though the intensity and duration of the action

varies slightly in different organs. There is no indication that the peripheral mechanism becomes fatigued on repeated administration of the substance, for with repeated administration there may be repeated constriction of the blood-vessels.

*Central Nervous Action*—Since perfusion experiments failed to show any change in reaction of the peripheral vessels in any organ after repeated injections, it seemed that the fall in pressure must be due to a central action. Sollmann and Pilcher,<sup>5</sup> in their experiments on the central nervous action of drugs, have shown that pituitary extract



Fig 2—Effect of consecutive injections of equal amounts of pituitary extract on blood pressure of rabbit

may cause a dilatation of the splenic vessels by reason of an action on the nervous system. By the use of a similar method, it was hoped to determine whether the fall in blood-pressure after repeated injections of pituitary extract was due to an increase of this dilator action of the central nervous system or to a diminution of the peripheral constrictor action. In this work, dogs not exceeding 12 kilos were used. Artificial respiration was given during the first part of the experiment. The

<sup>5</sup> Sollmann and Pilcher. *Jour. Pharmacol. Exp. Therap.*, 1910, 1: 571.

thorax was opened and the heart was placed in an oncometer, after which the thorax was closed and the volume changes of the heart recorded during natural respiration. The carotid was exposed for recording the blood-pressure. The kidney was brought to the surface through as small an opening as possible. The fatty mass around it was carefully removed and the vein and artery were exposed, care being taken to preserve from injury the nerves running along the vessels. The renal artery was clamped off near the aorta and cut. A cannula was inserted into the renal end. The vein was then ligated and cut peripherally to the ligature. The fibrous capsule of the kidney was partially removed. The kidney, which was connected with the body only through the nerve supply, was then perfused with a rhythmical stream of Locke's solution and the oscillations recorded by a Huithle manometer.<sup>6</sup> Pituitary extract

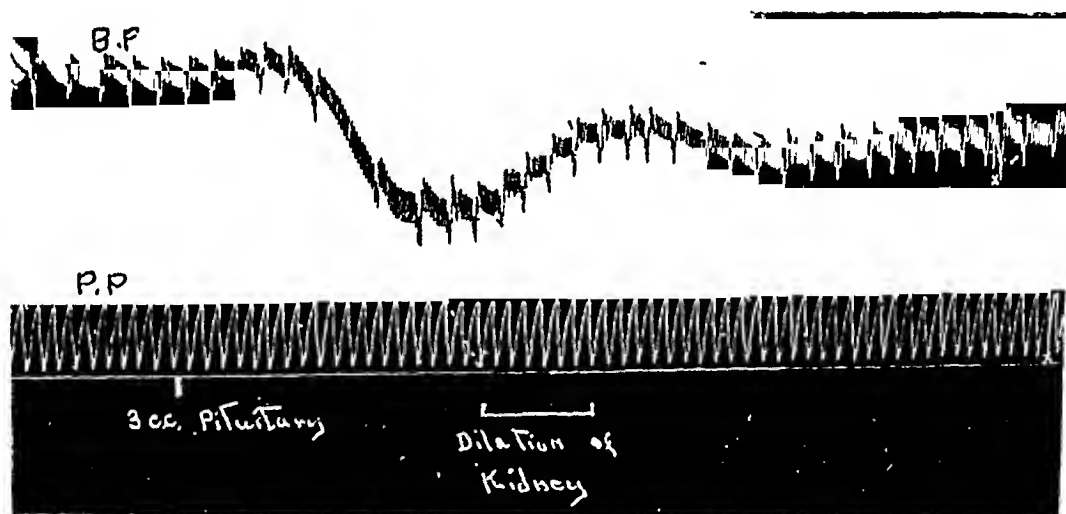


Fig 3—Perfusion of kidney with nerve supply intact. B, P, carotid blood-pressure, P P, perfusion pressure (after repeated injection of extract)

was now injected into the jugular vein. At the time the carotid pressure was highest, the diastolic perfusion pressure supplying the kidney fell slightly, indicating that a dilatation of the renal vessels had taken place through an effect on the vasomotor center. The perfusion was then discontinued to prevent the marked edema which occurs when the capsule is not removed. Repeated injections of pituitary extract were then given, until the animal reacted by a fall in pressure, as was shown by the carotid tracing. The perfusion was then resumed. On a further injection of the pituitary extract into the jugular vein, a dilatation of the vessels and a fall in carotid pressure took place, and at the same time a dilatation occurred in the vessels of the perfused kidney (Fig 3). This dilatation, however, was not increased over that which occurred with

the rise in blood-pressure during the first part of this experiment, this fact would indicate that the fall in blood-pressure is not due to an increase of the dilator action of the central nervous system. This is further substantiated by the fact that the dilatation of the renal vessels comes on after the maximum fall in blood-pressure has been reached, and, in this case, the carotid pressure shows no indication of having been influenced by the nervous system (Fig 3)

#### V THE EFFECT ON THE HEART

Since it appears that the subsequent fall of blood-pressure after repeated injections of pituitary extracts is not due to a fatigue of the peripheral vessels, nor to a heightened influence of the dilator effect of the central nervous system, the influence exerted by the heart on the blood-pressure was next determined.

The conclusions as to the influence of pituitary extract on the heart were based on the results obtained from 249 injections into the living animal (dogs, rabbits) and from the perfusion of eighteen rabbits' hearts

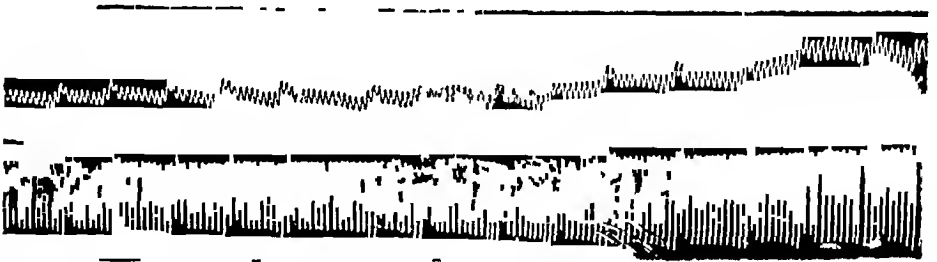


Fig 4—Effect of pituitary extract. Rise in blood pressure (below) accompanied by a gradual depression of the heart. (Reduced to two-thirds original size.)

In considering the effect on the amplitude of the heart's contraction, only those experiments were utilized in which actual cardiac tracings were obtained. Changes in the oscillations of the blood-pressure, which have been interpreted by some investigators on this subject as characteristic of changes in the heart's action, were not accepted as such by us.

*Perfusion Experiments*—Locke's solution was used for the perfusion of the heart. The ventricular pressure was recorded by means of a cannula pushed through the semilunar valves of the pulmonary orifice, down into the right ventricle, this cannula being connected with a tambour. The auricular pressure was recorded in a similar way through the inferior vena cava. The perfusion fluid passed out through the superior vena cava, a cannula was placed in this vessel and was elevated to that height which would give a hydrostatic pressure proper to insure the recording of the auricular changes through the inferior vena cava. The effects attending these experiments on the amplitude and rate of the heart-beat may be summarized as follows:

**Amplitude** Ninety-four per cent of injections caused a decrease in amplitude, 6 per cent of injections caused no change in amplitude, one experiment gave an increase in amplitude

**Rate** Seventy-five per cent of the hearts were slowed, 25 per cent of the hearts were not affected, at no time was the rate increased

In the living animal neither the rate nor the amplitude of the heart-beat shows the constancy that is found in the perfused hearts. The heart is affected by the pituitary extract through several avenues. A vagus influence is exerted and there is a direct action on the heart muscle as well. These two factors, with combinations of the two, create a complex set of variations in rate and amplitude. The scope of this paper does not permit of the discussion of these variations of the heart's action *per se*, but only as they affect the blood-pressure. For the present purpose it is sufficient to say that in the greatest number of these experiments the heart's rate was moderately slowed early in the drug's action and remained so throughout the experiment. The remaining small per-

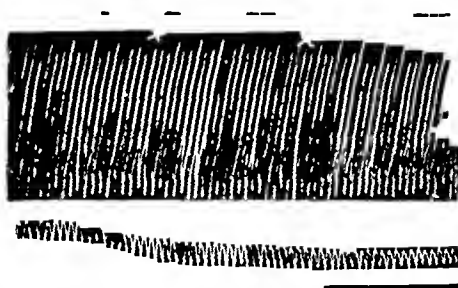


Fig 5—Cardioraph tracing (above) showing a strengthening of the heart, with a fall in carotid pressure (below)

centage of experiments is made up of the total of cases in which the rate was not affected, cases in which the rate was increased, and cases in which the rate was increased early but later gave way to a slowing. Similarly, the amplitude of the heart's action after the administration of pituitary extract showed an early gradual depression which was typical. The chief variations were a strengthening action occurring early and a strengthening action occurring late. These various actions on the heart are responsible for the following definite changes in the shape of the blood-pressure tracing

1 When the amplitude and rate of the heart are gradually decreased from the start, as in typical experiments, the changed cardiac output is not shown in the blood-pressure tracing, except that the rise of the curve as a whole is less pronounced (Figs 1 and 4)

2 Where the myograph tracing shows a marked and sudden depression of the heart, due to the action of pituitary extract, the blood-pressure shows a notch, occurring as the summit of the pressure height

is reached, varying in size and extent in proportion to the extent and duration of the heart's depression (Fig 1 *B*)

3 When the heart is strengthened during the early action of the drug, no notch is seen in the blood-pressure curve, and there is no indication of the heart's action

4 The strengthening of the heart which occasionally occurs late in the drug's action, coming on after the height of the blood-pressure curve has been passed and a fall is taking place, shows on the downward limb of the blood-pressure tracing as a transient and very temporary increase in pressure (Fig 1 *C*)

5 Cases sometimes occur in which an early cardiac depression causes first a notch or hump in the blood-pressure curve, while a later strengthening of the heart's action produces a second notch and hump Careful

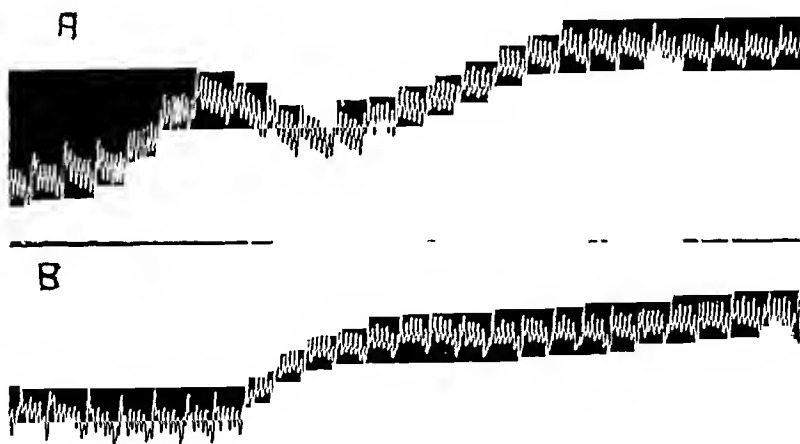


Fig 6—A, effect of 2 cc of pituitary extract mixed with 50 cc of blood drawn from the animal B, effect of 2 cc alone

scrutiny of the curves indicates, however, that these depressions in the blood-pressure are not the same either in conformation or in time as those obtained after repeated doses of pituitary extract (Compare Fig 2 *F* with 1 *B* and 1 *C*)

It has been suggested by Wiggers<sup>1</sup> that the depressor action of pituitary extract might be due to an increased weakening of the heart. This suggestion has not been borne out by this work. In the first place, the weakening of the heart, as has been seen already, is not constant, and the fall in blood-pressure may occur even when the heart is strengthened (Fig 5). In the second place, the depression in the action of the heart is not greater than with the first injection. Third, the time relations between the depression of the heart's action and the beginning of



the fall in pressure are not synchronous. These facts taken together exclude the possibility of attributing the real fall in pressure which is typical of repeated injections to the cardiac depression.

## VI THE BLOOD

Blood-pressure tracings, illustrating the effect of repeated injections of pituitary extract, show a gradation from the sharp, abrupt rise in pressure following the first injection, through a number in which the rise in pressure gradually becomes less marked and less abrupt, until the tracings are reached in which an actual fall of pressure is observed. So uniform and constant are these gradations, as the blood becomes more saturated with the substance, that a change in the drug brought about by the action of the blood itself was looked on as the last possible cause for its diminished activity and the fall in pressure. To test this possibility, however, several experiments were performed.

**EXPERIMENT 1**—Sixty cc of blood were drawn from the femoral artery of a dog. This blood was defibrinated and filtered. Two cc of pituitin were mixed with the blood, and the mixture was allowed to stand for from twelve to fifteen minutes. The blood and pituitin were then injected into the animal through the jugular vein, the blood pressure being recorded from the carotid artery. There occurred in every case a fall in pressure, followed by a rise (Fig. 6). Both the fall and the rise in pressure due to the drug were somewhat masked by the rise in pressure due to the increased volume of blood. This action took place when the blood-pituitin injection was given, but was much more pronounced if an injection of pituitin alone was given previously. As a control, an equal quantity of pituitin in an amount of salt solution equalling that of the blood was injected after the injection of the blood-pituitin. The result was a sustained rise in blood pressure.

**EXPERIMENT 2**—The femoral artery was exposed and a cannula placed in its ramaprofunda. A bandage was placed loosely around the thigh as high up as possible. The femoral artery was then clamped off above, and 2 cc of pituitin were injected into the ramaprofunda. The femoral artery was released and the bandage drawn tight, so that the return of blood to the rest of the body was cut off. In this way, the extract was mixed with arterial blood and distributed to the greater part of the limb. At the end of from ten to fifteen minutes the bandage was cut and the blood allowed to flow into the general circulation. A fall in pressure occurred, together with a slowing of the heart. When a limb was similarly bandaged, but without pituitin injection, there was no change in pressure when the bandage was released.

**EXPERIMENT 3**—A limited number of experiments were carried out in which the kidneys were perfused with blood. Pituitin was injected into the living animal until the blood pressure fell. The blood was drawn and defibrinated. A mixture of two parts of blood to one part of salt solution was used both as perfusing medium and as the solvent for the pituitary extract. In this way the specific gravity and viscosity of the perfusing medium and of the material injected into the medium were the same, thus excluding any change which might be attributed to altered viscosity. Kidneys thus perfused showed a dilation of the blood vessels when pituitary extract was injected.

Since this work has been completed, Cushing and Goetsch,<sup>7</sup> working with the cerebral fluid from patients with tumor of the hypophyseal

<sup>7</sup> Cushing and Goetsch. *Am Jour Phys*, 1910, LVII, 60.

region, have obtained blood-pressure curves following injections of this cerebral fluid, which they believed to contain the secretion of the pituitary gland. These tracings are very similar to the tracings obtained by us in experiments above, series one and two.

From these experiments it seems clear that whenever the pituitary extract is present in the blood or lymph in sufficient concentration, the usual action of the extract is reversed so that the substance causes a dilatation of the vessels and a fall in the pressure.

#### CONCLUSIONS

1 The depressor action of pituitary extract elicited by repeated injections is not due to the fatigue of any peripheral mechanism, nervous or muscular. Perfusion experiments indicate that it constricts all the blood-vessels of the body by a direct action on the muscles of the arterioles, and often repeated injections show practically no decrease in the constrictor reaction.

Organs removed from animals giving only a depressor reaction with pituitary extract show on perfusion with the extract in Locke's solution the typical constriction of their vessels.

2 The depression of blood-pressure following numerous injections of pituitary extract is not due to an overbalancing of peripheral constriction by a central dilator influence. Such a counteracting dilator influence of central origin is always weak and no more pronounced after repeated than after the initial reaction, and moreover it does not come on until the fall of pressure is at its lowest.

3 Sudden depression or slowing of the heart, though occasionally showing as a notch in the blood-pressure records, is not the cause of the typical drop in pressure obtained after repeated injections, for such depression is not similar either in conformation or in time to the depression obtained by the latter means, and may in fact exceptionally occur with a strengthened heart.

4 Experiments indicate that when the blood becomes sufficiently saturated with pituitary extract, an interaction takes place which converts its constricting action on the peripheral vessels into a dilating one.

## OBSERVATIONS ON THE HEMOLYTIC SKIN TEST FOR CANCER

LOUIS M. WARFIELD, M.D.  
MILWAUKEE, WIS.

In February, 1910, appeared an article by Elsberg, Neuhof and Geist<sup>1</sup> describing a skin reaction in carcinoma from the subcutaneous injection of human red blood-cells. The results which they obtained were so remarkable that, were they correct, we should have probably the most valuable test yet discovered for the diagnosis of carcinoma. The test, in brief, consists in the subcutaneous injection of 5 minims of a 20 per cent suspension of washed human red cells into the flexor surface of the forearm of the individual suspected of having cancer. A positive reaction consisted in the appearance within six hours of a "somewhat irregular oval area with a well-defined margin measuring from 1 by 2 cm. to 3 by 5 cm. The margin is often surrounded by a whitish areola. The color of the lesion varies from a brownish-red to a maroon with, rarely, a bluish tinge. The lesion is distinctly raised from the surrounding skin surface. At times this elevation is so slight that careful examination in good daylight is necessary to recognize it. When the lesion has disappeared, there remains behind a flat yellowish or greenish discoloration such as is left by any small ecchymosis."

Up to the time of publication they had made 684 injections on 432 patients with the following summarized results. A positive reaction was found in 90 per cent of patients with carcinoma (excepting the very advanced). No reaction was observed in 94 per cent of patients suffering from other diseases. A reaction of this nature would undoubtedly be of inestimable value in the diagnosis of obscure cases where cancer was suspected.

The source of the corpuscle suspension was described in detail and hedged about with numerous restrictions. "Tuberculosis and syphilis must be excluded, the patient must not only be free from any evidence of disease, but must not have been recently ill, nor have received any injury, must not have had even the slightest operation, and must not have recently had an anesthetic. The blood can, however, be taken from a patient during the early stages of ether anesthesia." They obtained their blood from children in hospital who were to be operated on for hernia.

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\*From the Clinical Pathological Laboratory of the Milwaukee County Hospital.

1. Elsberg, Neuhof and Geist. *Am. Jour. Med. Sc.*, 1910, cxxxix, 264.

It was a very interesting suggestion of Elsberg that hemolysis of human red blood-cells be tried not on serum of cancer patients but *in vivo*, the foreign red cells there being bathed in plasma so that any amount, however small, would be brought to the part and produce the hemolysis. The suggestion would undoubtedly have proved of great value, had it been founded on actual, accurate results with hemolysis *in vitro*. I shall examine the evidence now accumulated in regard to the specificity of the hemolysis of human red blood-cells by serum of cancer patients, and then I shall briefly relate the results of personal experiments.

#### I GENERAL REVIEW OF HEMOLYTIC EXPERIMENTS

Engel,<sup>2</sup> and later Mertens,<sup>3</sup> could not prove the existence of specific antibodies (*Kiebsubstanzen*) in the serums of cancer patients. Fischel<sup>4</sup> found that in about one-half of cases of malignant tumors, the serum had an increased hemolytic power compared with serum from normal persons. He worked with human serums and red cells of chickens. He showed similar hemolytic power in serums from cases of diabetes, pernicious anemia, chronic endocarditis and tuberculosis. Weil,<sup>5</sup> using human red blood-cells, found results absolutely in accord with those of Fischel. The reaction is not specific for tumors (cancers).

Crile,<sup>6</sup> however, was led to test the blood serum of cancer patients against suspensions of normal human red cells, although it was known that there was no specific hemolytic reaction. His results were most astounding. For example, up to 1908 he had studied 591 cases. Of these, 211 serums of normal individuals showed no hemolysis. In 153 cases of cancer there were 85 per cent positive hemolytic serums. But in 92 per cent of cases of tuberculosis there was reversed hemolysis, i. e., normal serum hemolyzed the corpuscles of the tuberculous patients. This work of Crile has not been confirmed, on the contrary, no one has been able to obtain such constant results in hemolysis.

R. Weil<sup>7</sup> states that human serum in various diseases is occasionally hemolytic toward the corpuscles of other human individuals. He found that extracts of lymphosarcoma of dogs were not hemolytic for dogs' corpuscles, but necrotic tumors possessed a high hemolytic power. He further showed that in some dogs with necrotic tumors, the serums were hemolytic in some degree for all dog red corpuscles. Normal dog serum is rarely hemolytic.

2 Engel, C. S. *Deutsch med Wchnschr*, 1903, **xxix**, 897.

3 Mertens, V. E. *Deutsch med Wchnschr*, 1904, **xxx**, 203.

4 Fischel, W. *Berl klin Wchnschr*, 1908, p. 882.

5 Weil, R. *Jour Am Med Assn*, 1908, **li**, 158.

6 Crile. *Jour Am Med Assn*, 1908, **li**, 2036.

7 Weil, R. *Jour Med Research*, 1908, **xi**, 281.

Ottenberg and Epstein<sup>8</sup> performed many tests with serums of patients on washed red corpuscles of other patients, in an attempt to test the value of the hemolytic reaction in cases of cancer. Their experiments were performed in groups, every serum being tried in turn on the washed red cells of every other number of the group. While they found that the serums of subjects with malignant tumors were hemolytic in 76 per cent, in all other diseases tried the serums were hemolytic in 50 per cent. They say, "as a result of this work, the chief object of which has been to determine the value of isohemolytic reactions in diagnosis, we are forced to the unsatisfactory conclusion that the method is not at present to be relied on for diagnosis."

In a further attempt to show the presence of hemolysins in body fluids, R. Weil<sup>9</sup> tested the lytic reactions of ascitic fluids from cases of spontaneously cured cancer (Hodenpyl's case), from other cases of long standing, apparently quiescent, cancers and fluids of transudates. He used the red cells of fifty-three persons of whom twelve had cancer. "All of the fluids occasionally manifested hemolytic properties, and, in the case of some, this was more general than in others. It was not, however, possible to distinguish the cancerous fluids in any way by their mode of reaction, despite the fact that the blood serum of cancerous individuals has, in general, been found by previous workers to possess more marked hemolytic properties than the normal."

The general conclusions reached by all investigators except Crile is that there is nothing specific in the hemolysis of normal human red cells by the serums or cancerous fluids of patients suffering from cancer. Such a reaction is not available as a means of diagnosing cancer, although serums of patients with necrotic tumors (cancers) do seem to have a marked hemolytic power on normal red cells.

## II PERSONAL OBSERVATIONS

The results of the observations made on seventy-four patients suffering from a variety of diseases, including carcinoma, are graphically shown in the tables. The last table is a summary of the work. The blood was taken from perfectly healthy young adults, washed in several changes of normal salt solution and made up to the desired percentage suspension.

It seemed possible that several factors might influence the reaction *in vivo*. (1) The volume of injected suspension, (2) the concentration of the suspension, and (3) the relation of the subcutaneous tissue to the skin, that is, whether the skin was loosely or tightly adherent to the subcutaneous tissues. Several injections of red cells hemolyzed with distilled water were made in order to see what appearance would result, as it

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8 Ottenberg and Epstein THE ARCHIVES INT MED, 1909, III, 467

9 Weil, R. Jour Med Research, 1910, XXXIII, 85

TABLE 1—OBSERVATION 1—SIXTEEN CASES

Blood from white, healthy male, 21 years old, one month after uncomplicated operation for strangulated hernia      Site of injection, forearm flexor surface, amount 5 ml/mls, 20 per cent suspension      Time 2 p m

No	Hosp No	Diagnosis	Appearance After Six Hours	Appearance After Twenty-Four Hours
1	7615	Mitral stenosis	Pinkish, slightly raised oval area, 2x5 cm	Purplish discoloration of spot
2	7834	Arteriosclerosis	Absolutely no evidence	Same
3	7822	Otitis media	Absolutely no evidence	Same
4	7809	Rheumatic fever	No evidence	Very slightly raised oval pink area, 1 5x4 5 cm
5	7530	Tuberculous hip	Slightly raised pink oval spot, 2x3 cm	Slight bluish discoloration considerably raised and firm
6	7688	Rheumatic fever	No evidence	Same
7	7832	Lead colic	Slightly pink raised oval spot, 1 5x3 cm	Purplish discoloration, raised slightly, 4x6 cm
8	7663	Carcinoma stomach	No evidence	Spot 3x5 cm like bruise, not raised. May have been early reaction
9	7826	Sarcoma shoulder	Slight discoloration pinkish, 2x3 cm	"Black and blue" level spot like Case 8
10	7780	Tuberculous hip	No evidence	Same
11	7768	Gunshot wound, arm	No evidence	Same
12	7806	Secondary cancer, liver	No evidence	Same
13	7583	Typhoid convalescent	Very positive      Bright pink oval raised, 2x5 cm	Oval "black and blue" spot, 4x6 cm
14	7562	Carcinoma stomach, cachectic	No pain	No evidence
15	7746	Carcinoma stomach (?)	Oval, pinkish, slightly raised, 1x2 cm	Slight discoloration, purplish green, 3x1 5 cm
16	7640	Typhoid convalescent	Oval, bright pink, 1 5x3 5 cm      Slightly raised	Slight "black and blue" spot

TABLE 2—OBSERVATION 2—NINETEEN CASES

Blood from same man, 4 days old, no laking seen Site of injection, forearm Amount injected 5 minims Time 11 a m

No	Hosp No	Diagnosis	Appearance After Six Hours	Appearance After Twenty-Four Hours
1	7701	Tabes dorsalis	Slightly raised, not discolored	Flat pink spot, 3x5 cm
2	7812	Tabes dorsalis (?)	No evidence	Very faint, slightly greenish brown spot
3	7427	Arthritis deformans	No evidence	No evidence
4	7745	Syphilitic ulcer, leg	Very slight brown discoloration, very slightly raised	Slight brownish discoloration
5	7681	Gonorrheal rheumatism	No evidence	Only very faint brown spot, 2x3 cm
6	7795	Chancroids	No evidence	As above
7	7831	Tertiary syphilis	Very slight greenish brown discoloration, slightly raised	Flat slight greenish spot, 2x4 cm
8	7630	Syphilitic ulcer, leg	No evidence	Slight reddish spot, 2x3 cm
9	7788	Gonorrheal rheumatism	No evidence	Small "black-and-blue" spot
10	7786	Gonorrheal rheumatism	Slight brownish discoloration, 3x1.5 cm, slightly raised	Brownish green spot
11	7759	Myocarditis	Nothing	Nothing
12	7474	Blastomycosis	Dirty brownish discolored area	Greenish spot 2x4 cm
13	7718	Traumatic myelitis	No change of color, slightly raised	Very slight pink, 2x4 cm
14	3521	Spastic paraplegia	Nothing	Slight pinkish purple spot, slightly raised, some what tender
15	29	Tabes	Purplish red discoloration, 1x5 cm, slightly raised	Nothing seen
16	7132	Spastic paraplegia	Very slight lilac spot slightly raised, 2x4 cm	Very tender, large pinkish area, slightly raised
17	7529	Multiple sclerosis	Slightly sensitive, slightly raised, no color	Slightly tender and raised, light pink color
18	2020	Traumatic myelitis	The faintest pink color, very slightly raised	Same Slightly tender
19	7667	Gout	Raised, soft, slightly mottled, irregular oval area, tender	Same

TABLE 3—OBSERVATION 3—SIX CASES

Blood from athletic white man, well for years, aged 25 Five injections of blood suspension, (a) two into left forearm, (b) two into right forearm, (c) one, skin over biceps,\* (a) 5 and 10 minims of 20 per cent suspension, (b) 5 and 10 minims of 10 per cent suspension, (c) 5 minims 20 per cent faded in distilled water, injected 11 a m, examined 5 p m

No	Hosp No	Diagnosis	a 5	a 10	b 5	b 10	Remarks
1	7637	Carcinoma stomach	0	0	0	0	Irregular brownish red spot
2	7679	Tuberculous hip	0	Slight	0	0	Irregular brownish red spot, 3x5 cm
3	7619	Fracture foot	0	+	0	0	Brownish red bruised spot
4	7863	Sprained ankle	0	+	0	0	As above
5	7856	Lumbago	0	+	0	+	As above
6	7602	Ulcer leg	0	+	0	+	As above

\* All areas showed dark bluish black discoloration after six hours

++ denotes considerable discoloration of black and blue appearance

+ denotes very slight discoloration of black and blue appearance

TABLE 4—OBSERVATION 4—SIX CASES

Blood from healthy white female, well for years, aged 22 Four injections of corpuscle suspension, (a) two into left forearm, (b) two into right forearm, (a) 5 and 10 minims 20 per cent suspension, (b) 5 and 10 minims 40 per cent suspension, injected 11 a m, examined after six and twenty four hours

Number	Hospital No	Diagnosis	a 5		a 10		b 5		b 10		Remarks
			6 hours	24 hours	6 hours	24 hours	6 hours	24 hours	6 hours	24 hours	
1	7835	Rheumatic fever	—	++	—	++	—	++	—	++	+ is very slightly brownish-green color
2	7846	Rheumatic fever	—	++	—	++	—	++	—	++	+ is faint slight greenish color
3	7851	Rheumatic fever	++	++	++	++	++	++	++	++	All showed large, distinct greenish-brown flat spots, fading off into normal skin
4	6674	Arthritis deformans	+	+	—	+	+	+	—	+	Five minims given near wrist, where skin is rather tight All showed only small, not very distinct brown
5	7575	Aortic Insufficiency	—	+	—	+	+	+	+	+	Right arm showed colored spots, left arm nothing, all after twenty-four hours showed discoloration
6	7842	Stilette small intestine (tuberculous)	—	+	+	+	—	+	+	+	Ten minims more distinct than 5 minims

TABLE 5—OBSERVATION 5—SIX CASES

Blood from healthy male, aged 26, taken March 25, 1910, used March 28, 1910 Four injections Two of 20 per cent suspension, 5 m left forearm near elbow, 10 m near wrist, two of 40 per cent suspension, 5 m right forearm near elbow, 10 m near wrist Injected 10 30 a m Examined after six and twenty-four hours

No	Hosp No	Diagnosis	Appearance After Six Hours		Appearance After Twenty-Four Hours
1	7902	Influenza	Marked, 4x5 cm, bright reddish green spot lower right Very slight greenish upper left not so marked Upper left very slight, but more distinct than upper right Distinct discoloration lower right, less upper Slightly seen on lower left Nothing upper left Nothing seen at any spot		All spots brownish blue, rather dark, very distinct, lower right more marked
2	7823	Pneumonia, delayed resolution	Nothing seen at any spot		All slightly greenish and alike
3	7796	Typhoid convalescent	Nothing seen at any spot		All slightly pale green, left trifle more
4	7801	Typhoid convalescent	Only on upper right arm very slight pink area, others nothing		Only right upper one shows slight green color
5	7784	Typhoid convalescent	Nothing seen at any spot		All show pale, light green, diffuse stain, right more than left
6	7802	Typhoid convalescent	Nothing seen at any spot		All show slightly pale green diffuse stain



TABLE 6—OBSERVATION 6—EIGHT CASES

Blood from healthy white female, aged 23 Site of injection, upper left arm over bleeps Amount 10 minims Suspension 20 per cent corpuscles  
Time 10 30 a m, April 1, 1910 Examined after six and twenty-four hours

No	Hosp No	Diagnosis	Appearance After Six Hours	Appearance After Twenty-Four Hours
1	7842	Tuberculous striature intestine	Raised purplish brown, slightly painful, 3x5 cm	Black and blue, slightly raised
2	7716	Cirrhosis liver	Considerably raised Color, size as above Painful	Large, hot, swollen, tense area, painful, brownish purple
3	7640	Typhoid convalescent	Raised, purplish-brown spot, slightly tender, 2x3 cm	Black and blue flat, 3x5 cm
4	7694	Tuberculous hip	Slight brownish spot, slightly tender	Slight greenish spot, flat, no tenderness, 2x3 cm
5	4346	Chronic tuberculous osteomyelitis	Brownish purple flat spot, 3x5 cm No tenderness	Black and blue spot, flat, no tenderness
6	7826	Sarcoma (low)	Nothing seen, only slightly raised, slight tenderness	Slight greenish spot, slight tenderness, 2x3 cm
7	7529	Fracture patella	Very slight brownish pink, slightly raised spot, 3x5 cm	Large, 8x6, purplish-red, raised area tenderness
8	7618	Fistula in ano	Slight soreness Otherwise nothing	Slight pink spot, 1x3 cm Slight tenderness

TABLE 7—OBSERVATION 7—THIRTEEN CASES

Blood from same person as Observation 6 Site, right forearm Amount 10 minims Suspension 20 per cent corpuscles Time 11 a m, April 8, 1910 Examined after six and twenty-four hours

No	Hosp No	Diagnosis	Six Hours	Twenty-Four Hours
1	7907	Gout and tuberculous	Nothing	Nothing
2	7823	Delayed resolution, pneumonia	Nothing	Greenish spot, 3x5 cm
3	7914	Chronic bronchitis	Scarcely visible greenish spot	Same
4	77867	Tuberculous, lung	Nothing	Nothing
5	77171	Epithelioma, face	Purplish spot, not raised sharply defined, 2x3 cm	Same but darker color
6	77898	Carcinoma peritoneum	Same appearance as No 5	Same size but more green color
7	77715	Clinical rheumatism	Nothing	Nothing
8	76152	Epilepsy	Very light slate colored spot	Same
9	74218	Tuberculous	Slightly raised, purplish spot, 4x5 cm	Same
10	75999	Psoas abscess	Flat, slightly reddish spot	Same
11	77817	Umbilical hernia	Slightly raised bluish spot, differs in color from Nos 5 and 6	Slate blue spot, 3x4 cm Faint light green spot
12	77929	Cirrhosis liver	Nothing	Very faint light green spot
13	77925	Cirrhosis liver	Nothing	Very faint light green spot, 4x6 cm

R refers to women, all others men

seemed doubtful whether injections beneath the skin into the subcutaneous tissues would show through the skin. This at once raises the question of the value of a color reaction, for some skins are much thinner and more transparent than others. As the table shows, all such injections revealed marked discoloration. Again, it is doubtful if any large amount of plasma can come in contact with the injected red-cell suspension. The injection is a foreign substance, and the body cells must react toward it as they do toward any foreign substance. That some action does take place at times seems certain, because there are times when there is evidence that the hemoglobin of the injected cells has been released into the tissues. The curious "black-and-blue" spot simulating ecchymosis from a bruise seems to prove this. On the contrary, in certain persons the injected cells must be absorbed very quickly, for there is no evidence to reveal the injection. No explanation is offered for these phenomena.

It is evident from a perusal of Tables 1 and 2 that there is no regularity in regard to the hemolytic reaction. The statement of Weil is

TABLE 8—SUMMARY OF SEVENTY FOUR CASES FROM PREVIOUS TABLES

Disease	No Cases	Pos	Neg	% Pos	% Neg
Carcinomas, epitheliomas	7	3	4	42.8	57.2
Rheumatic fever	5	1	4	20.0	80.0
Convalescent typhoid	8	4	4	50.0	50.0
Tuberculosis	9	3	6	33.3+	66.6+
Cirrhosis liver	3	1	2	33.3+	66.6+
Cancer liver, secondary	1	0	1	0	100
Sarcomas	2	1	1	50	50
Blastomycosis	1	1	0	100	0
All other diseases	38	10	28	26.3	73.7
Totals	74	24	50	32.4	67.6

borne out, namely, that human serum in various diseases is occasionally hemolytic toward the corpuscles of other human individuals. He was working with serum and corpuscles, but the same statement may be made in regard to hemolysis *in vivo*.

In Tables 3, 4 and 5 are shown the results of injecting 5 and 10 minims of suspension from 10 per cent to 40 per cent into the loose tissue of the mid-forearm and into the more adherent tissue near the wrist. No greater differences were noted than were found by using the recommended 5 minims of the 20 per cent suspension. What differences there were, were so irregularly distributed that no information could be gained on the points noted above.

On the contrary, Table 6 seems to show that 10 minims of a 20 per cent suspension caused more so-called positive reactions than 5 minims of a similar suspension.

This may have been simply a coincidence. At any rate, no importance is attached to it. This injection was given in the skin over the biceps.

There are seen fewer positive reactions in Table 7, using the same amount of a 20 per cent suspension of blood from the same person, than in Table 6. In Observation 7 the suspension was injected into the forearm.

A total of all the injections shows that 67.6 per cent were negative and 32.4 per cent positive. In spite of the fact that tuberculous persons are said to possess more isohemolysins than normal persons, the figures of a few cases show 66.6 per cent negative reactions. Leaving out the cases of malignant tumors, there are sixty-four cases with twenty positive and forty-four negative. This is quite different from the 94 per cent. negative reactions found in all other diseases by Elsberg, Neuhof and Geist.

In conclusion then, it seems evident that the same irregularities obtain in the hemolysis *in vivo* as that *in vitro*. The most evident point brought out is that the test cannot be said to be of any great value in the diagnosis of early carcinoma.

## RECOVERY OF A TYPHOID BACILLUS-CARRIER DURING VACCINE TREATMENT

WALTER V BREM, M D  
LOS ANGELES, CAL

AND F C WATSON, M D  
COLON HOSPITAL, CRISTOBAL, CANAL ZONE

Medical literature during the past five years has contained numerous reports of chronic typhoid bacillus-carriers, but there has been very little discussion of the treatment of these patients. The reason for this paucity appears to be that treatment has been unsatisfactory, and in but few cases has the infection been eradicated.

Dehler<sup>1</sup> has cured by cholecystostomy two patients who discharged the bacilli in the feces, but the bacilli did not disappear from the stools of a paratyphoid carrier on whom Forster<sup>2</sup> did cholecystostomy for gallstones. Grimme<sup>3</sup> reported the recovery of an intestinal typhoid carrier on whom cholecystectomy was done. Park<sup>4</sup> failed to eradicate the infection in "Typhoid Mary," an intestinal carrier, by the use of intestinal antiseptics and hexamethylenamin, the latter drug was given in doses of 100 to 150 grains daily. Park cites Lentz, who stated that he could not get rid of the bacilli by any treatment. Albert<sup>5</sup> reported the disappearance of bacilli from the urine of a carrier treated with hexamethylenamin, but no details were given and no statement made as to permanent recovery. Niepiaschk<sup>6</sup> had success with hexamethylenamin and boric acid (triborate of hexamethylenetetramin) in the treatment of a urinary carrier after he had failed with hexamethylenamin alone and in combination with resorcin. He gave this preparation in doses of 1.5 gm four times daily. Hammond<sup>7</sup> failed to cure an intestinal carrier to whom he gave hexamethylenamin for months.

Litterer<sup>8</sup> treated by vaccination a patient with a discharging typhoid bone lesion. He estimated that there were a half million bacilli in a

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\*From the Medical Clinic of Colon Hospital, Cristobal, Canal Zone.

\*Read in the Section on Practice of Medicine of the American Medical Association, at the Sixty-Second annual session, held at Los Angeles, June, 1911.

1 Dehler. *Munchen med Wchnschr*, 1907, liv, No 43.

2 Forster. *Verhandl d deutsch path Gesellsch*, 1907, p 163.

3 Grimme. *Munchen med Wchnschr*, 1908, lv, No 1.

4 Park, W H. *Jour Am Med Assn*, 1908, li, 981.

5 Albert, H. *Jour Am Med Assn*, 1908, li, 982. Discussion of Dr Park's paper.

6 Niepraschk. *Ztschr f Hyg u Infektionskrankh*, 1909, lxiv, 454.

7 Hammond, F S. *Jour Am Med Assn*, 1909, lii, 48.

8 Litterer, W L. *Jour Am Med Assn*, 1908, li, 982. Discussion of Dr Park's paper.

platinum loopful of the pus. He thought, justifiably, that the patient should be regarded as a chronic typhoid bacillus-carrier. Under vaccine treatment the patient showed great improvement, but was not entirely cured at the time of the report. He has recently informed us that this patient and another similar carrier were both cured by vaccination in three and two months, respectively.

Irwin and Houston<sup>9</sup> have successfully treated a urinary carrier by vaccination after failure with hexamethylenamin. The bacilli disappeared after the third dose and four subsequent examinations covering a period of two months were negative. Six vaccinations were given, the doses increasing from 50 to 1,000 million. Meader<sup>10</sup> treated successfully by vaccination a patient who discharged bacilli in her feces. The patient had had typhoid fever thirty years previously and had been exposed to infection five years previously. Before vaccination was begun, treatment was attempted with hexamethylenamin, 15 grains three times daily for two weeks were given, and then 75 grains daily. The large doses had to be discontinued after three or four days because of painful micturition. No diminution in the number of typhoid bacilli discharged in the feces could be detected. An attempt was then made to plant *B. coli* in the lower bowel in the hope that it would overgrow the typhoid organisms. Four doses, each about a pint, of a bouillon culture, were given per rectum. The typhoid organisms persisted in the stools and treatment with lactic acid bacillus tablets was tried, this also failed. Autogenous vaccines were then given at intervals of from one to two weeks. Six vaccinations were given, the doses increasing from 25 to 1,000 million, after which the stool cultures were negative on three separate examinations. Meader studied the bactericidal and agglutinating power of the blood during vaccination. The former rapidly rose, reaching its greatest power after 400 million bacilli were injected, it then fell rapidly, and seven days after 1,000 million bacilli were injected the bactericidal power had fallen to a point practically the same as when immunization work began. An interesting observation was that during the period of declining bactericidal power the agglutinating power became evident in dilutions of from 1 to 500 in one hour. The first stool examination that was found negative was seven days after the above phenomenon. No examination was made for twenty-three days previously, so it is difficult to correlate the disappearance of the bacilli with the serum phenomena. Meader seems inclined to think that the high bactericidal power of the serum was immediately correlated with the disappearance of the bacilli, but the stool was positive for bacilli only three days before the examination that showed the highest point of bactericidal power, and ten days after the previous

9 Irwin, S. T., and Houston, T. *Lancet*, London, Jan. 30, 1909.

10 Meader, F. M. *Bull. Johns Hopkins Hosp.*, 1910, xxi, 280.

during the administration of hexamethylenamin in combination with boric acid (triborate of hexamethylentetramin). One intestinal carrier recovered when lactic acid bacilli (*B. bulgaricus*) were implanted in the alimentary tract. One intestinal carrier apparently recovered after repeated exposures of the gall-bladder to x-rays. One intestinal carrier, two urinary carriers, and two carriers discharging bacilli from bone lesions have recovered during vaccination with autogenous vaccines. We shall add to the number one urinary carrier that recovered likewise during vaccination with autogenous vaccine. Altogether then, there have been only twelve recoveries of typhoid carriers as far as we have been able to find, six recoveries of intestinal carriers, four of urinary carriers and two of carriers with bone lesions. Including our own patient, six have recovered during treatment with autogenous vaccines.

#### CASE REPORT

Our patient was a little American girl, white, aged 4½ years. She had had an attack of fever, that was probably a mild initial attack of typhoid, in July, 1910, during which she was not under our care. She was admitted to Colon Hospital (No 26,236) Aug 3, 1910. She had a typical uneventful rather mild attack of typhoid fever, during which her serum in 1 to 50 dilution agglutinated the stock culture of *B. typhosus* in one hour. During the last fourteen days of convalescence she was given for prophylactic reasons 3 grains of hexamethylenamin three times daily—rather large doses for a small child. She was discharged from the hospital Sept 3, 1910.

On September 18, the child's mother was admitted to the hospital with continued fever, the onset having been about three days previously, or twelve days after the child's return home. *B. typhosus* was isolated by blood culture. The course of illness was typical of a rather severe attack of typhoid fever.

On September 19, the child's father was admitted with a mild remittent fever that persisted ten days, maximum 101.5 F. The onset of his attack was September 16, or thirteen days after the child's return home. A blood-culture, made after six days of fever and four days before the temperature remained normal, was negative. Although the patient had never had typhoid fever, two agglutination tests by Bass<sup>13</sup> macroscopic method were positive. There appeared a few quite definite rose spots. The spleen was not palpable. In the light of these facts and of subsequent events, it is quite certain that this was a mild attack of typhoid fever.

These two cases led us at once to suspect that the child was discharging typhoid bacilli in her urine or feces, and that she had infected her father and mother. Four examinations of her stools were all negative for *B. typhosus*. On the first attempt we failed, also, to obtain *B. typhosus* from the urine, but the second culture, Oct 7, 1910, was positive, and the organisms were isolated ten times thereafter without a failure until they finally disappeared, Feb 15, 1911, about six months after the attack of typhoid fever was over. Five successive negative examinations, covering a period of about three months, were then made.

Vaccination with autogenous vaccines was begun on Oct 10, 1910, and nine doses, increasing from 25 to 1,500 million, were given, the last on Feb 1, 1911, after which typhoid bacilli could no longer be isolated from the urine. The bacilli gradually decreased in numbers as vaccination proceeded. The first vaccine used (seven doses) was sterilized at 60 C for one hour, the second vaccine (two doses), at 53 C for one hour. The vaccinations gave slight local reactions

13 Bass, C. C. THE ARCHIVES INT. MED., 1910, VI, 717

only until the last injection of 1,500 million bacilli, when a mild general reaction occurred. The injection was given about 10 a. m., February 1, and at 8 p. m. the patient's temperature was 102. By noon the next day, the temperature had reached normal. During the entire time the patient seemed in perfect health.

Numerous agglutination tests were made before, during and following the vaccination period. Before vaccination the patient's serum in a 1-to-40 dilution gave a positive reaction in one hour against a suspension in salt solution of a twenty-four-hour agar culture of her own organisms, and an incomplete reaction against the bacilli of a stock culture. Three days after the first vaccination the reaction against both strains was incomplete. Seven days after the second vaccination, a 1-to-50 dilution of serum agglutinated the urine culture in one hour, but the reaction was negative in one hour against the stock culture, which, however, was agglutinated in six hours by dilutions of serum up to 1 to 200. After the seventh vaccination (400 million bacilli), the serum in a 1-to-150 dilution agglutinated the stock culture in one hour, and in six hours the stock culture was agglutinated by a 1-to-1,000 dilution. At this time a 1-to-150 dilution of the serum failed to agglutinate the urine culture, and in six hours the maximum dilution that caused agglutination was 1 to 300. Vaccination was then suspended for thirty-five days, during which the agglutinating power of the serum decreased. After twenty-eight days a 1-to-150 dilution of the serum agglutinated both strains in six hours, but in the same time a 1-to-200 dilution gave an incomplete reaction against the stock culture and was negative against the urine culture. Vaccination was resumed Jan 10, 1911, and on Jan 21 a 1-to-150 dilution of serum agglutinated in one hour the urine culture, but gave an incomplete reaction against the stock culture. On Feb 1, 1911, the last vaccination (1,500 million bacilli) was given, and on February 15 the serum in a dilution of 1 to 1,000 agglutinated both organisms in six hours. On March 1, a 1-to-1,000 dilution still agglutinated the stock culture in six hours, but the reaction was incomplete against the urine culture. On March 24, nearly two months after the last vaccination, the serum in a 1-to-200 dilution agglutinated the stock culture in one hour, and a 1-to-400 dilution, in four hours.

Between the dates of Dec 6, 1910, and Jan 10, 1911 (see table), no vaccinations were given, and the agglutinating power of the serum against both the urine culture and the stock culture decreased. On December 17, a 1-to-1,000 dilution of serum was positive in six hours against the stock culture, but a 1-to-300 dilution was the maximum dilution positive against the urine culture. On January 3, a 1-to-200 dilution gave in six hours an incomplete reaction against the stock culture and a negative result against the urine culture. During the period of this decreasing agglutinating power of the serum, the number of bacilli in the urine not only failed to increase, but actually decreased from 32 per loopful of urine on December 17 to 5 per loopful on January 3.

At the time of the observations no records were made of the numbers of colonies on the plates, but our impression is that during the first two months the number remained approximately the same. On November 26, there were 92 colonies per loopful of urine, and, with one exception, the number decreased gradually thereafter—92, (18), 45, 32, 5, 2, 0.

Nov 26, 1910	92 colonies per loopful
Dec 9, 1910 (13 days' interval)	45 colonies per loopful
Dec 17, 1910 (8 days' interval)	32 colonies per loopful
Jan 3, 1911 (17 days' interval)	5 colonies per loopful
Jan 21, 1911 (18 days' interval)	2 colonies per loopful
Feb 11, 1911 (21 days' interval)	0 colonies per loopful

If the time intervals are all changed to two weeks and the number of bacilli are calculated for each examination according to the rate of decrease for each period, the following results are obtained: 92, 42, 20, 4, 2, 0. In other words, the decrease in the number of bacilli proceeded with almost mathematical precision, the number being reduced one-half every two weeks, excepting during the

third interval, when reduction was more rapid. A part of this reduction was not associated with an increasing agglutinating power of the blood serum, but with a decreasing power, nor did the reduction cease when the agglutinating power rose again with subsequent vaccination. The phenomena suggest strongly that antibodies produced by vaccination were not acting on bacilli in the urine, but that a chronic typhoid lesion that was discharging typhoid bacilli in the urine slowly healed under the influence of vaccination, probably as the result of the action of antibodies in the lymph or exudate on the bacilli in the lesion. That there were not antibodies sufficient even to inhibit growth in the urine was shown by inoculating the sterile urine, just after the disappearance of typhoid bacilli, with typhoid organisms from both the stock and urine cultures. Both organisms grew well, in spite of the fact that the agglutinating power of the blood serum at this time was 1 to 1,000 in six hours.

Our experience leads us to suggest, therefore, that the eradication of the infection of chronic typhoid carriers by vaccination is brought about by the gradual healing of a chronic lesion under the influence of antibodies produced by the vaccination. If the bacilli grow in secretions and excretions only, it does not seem that vaccination would be effectual. Hexamethylenamin or lactic acid bacilli might be effectual in such cases. The only other treatment that our patient received was four 5-grain doses of hexamethylenamin on December 6 and 7. The previous examination of urine, November 26, had shown 92 bacilli per loopful. This result had discouraged us, and we brought the patient to the hospital to give a trial to hexamethylenamin treatment. We obtained a specimen of urine and began hexamethylenamin treatment before the plates were incubated. On the following day, we found the number of colonies so reduced that we discontinued hexamethylenamin and resumed vaccine treatment. That the four doses of hexamethylenamin had no permanent effect on the bacilli was shown by the fact that the number of organisms was 45 per loopful two days after the drug was given.

There may be a question as to whether or not our patient should be considered a chronic typhoid carrier. According to the classification of Frosch,<sup>14</sup> she should be considered one. Frosch divided carriers into two groups: "those who excrete bacilli for less than three months, and those who excrete them for three months and longer. The latter class constitute the chronic bacilli carriers, the *Dauerausscheiderin* of the Germans" (Simonds). Our patient carried typhoid bacilli for about six months after the temperature of her typhoid attack remained normal, and, accepting Frosch's classification, she may be considered fairly as having been a chronic typhoid bacillus carrier.

The possibility cannot be denied that the lesion that discharged bacilli may have undergone spontaneous healing without regard to vaccination. We prefer to say, therefore, that our patient recovered during vaccination, rather than that she was cured by the treatment. In the light of what is known of chronic typhoid carriers and of the chronicity of post-typhoid lesions, however, it does not seem probable that recovery was spontaneous.

One other objection might be made. Some typhoid carriers, both urinary and intestinal, discharge the bacilli intermittently. It may be suggested with reason that the disappearance of bacilli in our case may have been due to an intermission. This is possible. But the bacilli were

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<sup>14</sup> Frosch, *Klin. Jahrb.*, 1908, xix, 537. Cited by Simonds, *J. P. Am. Jour. Med. Sc.*, Aug., 1910, cxl, 247.



present on eleven successive examinations covering a period of more than three months, they gradually decreased in numbers and finally disappeared, and they have been absent on five successive examinations covering a period of almost three months. The first urine examination made was negative for typhoid bacilli, but the result was probably due to faulty technic, for we had just begun making bacteriological examinations of stools and urines. It seems probable to us therefore, that our patient was a continuous chronic typhoid carrier, and that she made a permanent recovery during treatment with autogenous vaccines.

#### BACTERIOLOGICAL CONSIDERATIONS

*Isolation*—The method of isolation of typhoid bacilli from the urine was that of Endo<sup>15</sup>. Endo's medium is a heavy agar to which is added basic fuchsin, lactose and sufficient sodium sulphite to decolorize the fuchsin. The red dye, fuchsin ( $C_{20}H_{11}N_3HCl$ ), is an acid salt of rosanilin, a colorless leukobase. The acid component of the red rosanilin salt is easily reduced by sodium sulphite. When lactose-fermenting organisms grow on the above medium, the acid formed combines with the decolorized rosanilin and the colonies are stained red. The heavy agar medium is exactly like "ordinary" agar, excepting that 20 gm of agar-agar per 1,000 cc are used instead of 15 gm. To 1,000 cc of the agar medium are added lactose, 10 gm, basic fuchsin, 1.8 cc of a 10 per cent solution in alcohol, sodium sulphite, 25 to 40 cc of a 10 per cent aqueous solution. The sodium sulphite should be added until the red color has changed to a faint pink. The agar medium can be prepared in bulk to be kept in stock, but the fuchsin, lactose and sodium sulphite should be added just before pouring into the plates. One hundred cubic centimeters of the medium will make about four or five plates, which should be 12 to 15 cm in diameter. The plates are exposed to the air (covered with clean paper), for one hour, during which they harden and dry. One loopful or more of the material to be examined is then placed on the surface of the first plate, and with a sterile bent glass rod it is spread widely over the surface, the rod is then stroked over the surface of the second plate, then the third, and so on. The plates are covered, wrapped in paper to exclude light, and incubated for twenty-four hours. The colonies of the lactose-fermenting organisms are then red, while the colonies of non-lactose-fermenting organisms are colorless. The method thus furnishes an easy way of isolating typhoid, paratyphoid and dysentery bacilli. The organism that causes difficulty most frequently is *B. fecalis alkaliogenes*.

<sup>15</sup> Endo. Centralbl f Bakteriöl, 1904, xxv, 109. A transcription of Endo's article was kindly given us by Dr S T Darling, chief of the Board of Health Laboratory, Ancon, Canal Zone.

*Identification* —The organisms that we isolated from the urine were small, actively motile, Gram-negative bacilli. They formed small, 1 to 2 mm diameter, translucent colonies with a bluish refractility on agar plates. Litmus milk was slightly acidified by them and remained acid. There was an invisible growth on potato. No indol was formed in Dunham's peptone medium. Bouillon showed a general turbidity without pellicle or sediment. There was no gas formation in any of the semi-solid litmus sugar media, acid formed in dextrose, mannite, galactose and dextrin, there was no change in lactose, saccharose or inulite. The organisms were agglutinated by the serum of a typhoid patient (the child's mother) in a 1-to-50 dilution in one hour. After the child was vaccinated with her own organisms, her serum agglutinated a stock culture of typhoid bacilli in a 1-to-200 dilution in one hour and in a 1-to-1,000 dilution in six hours.

#### SUMMARY

1 The literature of the treatment of typhoid bacillus-carriers is reviewed. Eleven recoveries, excluding our case, have occurred. Five of these patients recovered during vaccination with autogenous vaccines.

2 Our patient was a white child, female, aged 4½ years. Shortly after her attack of typhoid fever, her father and mother were infected. Typhoid organisms in pure culture were isolated from the child's urine. Hexamethylenamin had been administered to the patient during two weeks of convalescence from the typhoid attack.

3 Practically the only treatment given was vaccination with autogenous vaccines. Nine doses were given, increasing from 25 to 1,500 million. The bacilli decreased gradually and disappeared after the ninth vaccination. Eleven successive urine cultures were positive for *B. typhosus* and then five successive cultures were negative.

4 The total duration of the bacilluria, from the time of normal temperature, was about six months. The patient appeared to be a continuous carrier.

5 It seems that the disappearance of the bacilli was not an intermission but a true recovery, brought about by the gradual healing of a chronic lesion under the influence of vaccination.

We wish to thank Col. W. C. Goigas, Chief Sanitary Officer, for permission to publish this report.

423 Security Building, Los Angeles

## SUBACUTE LIVER ATROPHY \*

LINDSAY S. MILNE, M.D.  
NEW YORK

Since the time of Vesalius (1514-64) a great profusion of types of liver disease have been described and each associated with a more or less definite train of symptoms, till the present time leaves us with the most confused ideas of the pathological processes at work in almost any case of jaundice. As a result the diagnosis of cases of long-continued jaundice, exclusive of those due to such obstructive causes as gall-stones, tumor growth, etc., leads inevitably into the tangled artificial classification of the various destructive lesions of the liver.

One fact is certain—that in the whole range of diseases of the liver, from acute yellow atrophy to atrophic cirrhosis, the cases present an extreme variation as regards duration, symptomatology and morbid anatomy, and it may equally be noted that great numbers of cases present features which preclude them from any of the usual subdivisions of liver disease.

Acute yellow atrophy, as is well known, is an extremely wide-spread rapid necrosis of the liver. The term "atrophy" is therefore a misnomer. The condition is certainly much more common than it has usually been considered and this perhaps is accounted for, as in the past its conception has been based on an altogether too classic picture both clinically and pathologically. The disease has, however, a wide latitude in its duration, clinical type and pathological appearances and the condition appears to be essentially dependent on the degree of hepatic destruction. Examples indicating the discrepancy in the tenure of life in such cases may be noted in records reported by Ladoli in which death occurred in thirty hours, Dorflei, in three days, Fischer, in ten days, Edgworth, in twelve days, McCallum, in fourteen days, Tileston, in seventeen days, Hall, in twenty days, Meder, in twenty-one days and Klob, in twenty-eight days, etc., and many cases are described of as long as forty days' duration. In children in particular, a protracted course is the rule. (In a previous communication<sup>1</sup> I have noted three cases in young children who presented histories varying between six and ten weeks, and I have observed two other cases which came to autopsy after a considerably more prolonged course.)

The latter merge gradually into what may be known as the subacute group, in which the subject apparently has had more recuperative power and the hepatic destruction has not been so extensive. Thus, if the destructive processes, from whatever source, chemical, bacteriologic, etc.,

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\*From the Russell Sage Institute of Pathology, New York.

1 Milne, Lindsay S. *Jour. Path. Bacteriol.*, Cambridge, 1909, vii, 161.

they may be derived, should be less extensive in their effects on the liver, the symptomatology corresponds more or less in degree.

Not only is the extent of liver destruction important but also the rapidity of its accomplishment. In atrophic cirrhosis for instance, the process is also wide-spread but as such relatively small portions are destroyed at one time, and also as the liver cells have time to regenerate and the system to adapt itself, jaundice does not necessarily appear.

Subacute atrophy, like acute yellow atrophy, is not a real atrophy, but the result of a necrosis and the subsequent inflammatory repair. As in the acute cases, the necrosis is more or less rapidly accomplished, and the longer duration of life in the subacute or recovery in the chronic cases depends largely on the amount of liver destruction and its recuperative power.

Age and sex apparently are of little importance, acute and subacute atrophy being relatively common in children, thirteen patients observed in the last three years varied in age between 4 years and 69.

The etiology of such conditions has occasioned a vast amount of speculation, the disease seems to follow so many conditions, to be so widely different in its clinical and pathological types, as to make one suspect no uniform etiological agent. Some cases show no apparent toxic substance in the liver, being sterile in culture, and emulsions of the liver being non-toxic to rats, rabbits or cats, as for instance, in a male aged 69 who died after a progressively intense jaundice of twelve days' duration. In another case, slightly more protracted, in a male aged 38, in which death occurred in an intensely jaundiced condition, a pure culture of *B. coli* was obtained from the liver and spleen. Emulsions of the liver and spleen injected into rats produced death within twenty-four hours, while injections of emulsions from the duodenum and large intestine produced no effect. A pure *B. coli* was again isolated from the livers and spleens of the dead rats, which again proved fatal to another series of rats, but produced no result on rabbits, dogs or cats. This, however, means very little as a variety of organisms can be obtained from the livers of subjects who have died from many different causes.

#### REPORT OF CASE

From an experience of ten cases in the last three years, five of which have already been published,<sup>1</sup> presenting histories lasting six weeks and upward, a further case may be noted in which the process was very prolonged and the diagnosis from ordinary cirrhosis presented difficulties even at necropsy.

*History*—The patient was a large, obese man, aged 41, a bar porter. His previous health and digestion had been apparently very good. He had been in the habit of drinking two or three glasses of whisky a day. There was no evidence or history of syphilis nor any indication of it in his family record. He denied malaria, scarlet fever, diphtheria, small pox, pneumonia, typhoid or any other special disease.

Sixteen months before the date of his death, his ankles became slightly swollen in the evenings. This swelling disappeared when he rested at night and was never sufficient to incapacitate him from his work. Six months after this, jaundice gradually appeared, although he felt at that time in very good health. A fortnight later, the jaundice suddenly became very intense, and there was marked distress in the epigastric region. This was diffuse in character and not colicky or related to the shoulder region, and was not associated with any gastro-intestinal disturbance. Immediately following this attack, and being as he said, not under the influence of liquor, he became very much prostrated and fainted. On admission to hospital he was intensely jaundiced, and the urine contained a considerable amount of bile pigment but no albumin, leucin or tyrosin. His heart was somewhat irregular in action, and there was a soft systolic murmur heard, best at the region of the apex. He remained in hospital for two months, his weight remaining constant and the temperature continuing normal. The jaundice almost completely faded and he was discharged, feeling in good condition. Six days later he was readmitted, as edema of the legs had returned and jaundice had again become intense. Ascites was also slightly evident. The liver at this date extended from the sixth right costal interspace to 1 inch below the costal margin in the right midclavicular line. Its lower border was firm and rather irregular and on palpation was slightly tender. The spleen was palpable 1 inch below the left costal margin, and a soft systolic murmur was noted over the apex of the heart. The blood showed no important changes except slight anemia, and the urine contained no albumin, but bile was present in small quantity. The feces were pale but did show some bile coloring. About a month later the patient developed a mild attack of facial erysipelas. For the next six months the jaundice continued gradually growing more intense. The temperature, except for some small irregularities and during the attack of erysipelas, was practically normal throughout. The leukocyte count averaged about 5 000 per cubic millimeter, rising to 14,600 coincidentally with the erysipelas. Ascites became very marked and the patient was tapped fifteen times during the last six months, large quantities of somewhat bile stained clear fluid averaging 1 010, specific gravity being removed. During the last month, the stools were quite clay colored, the patient's appetite completely failed and emaciation was rapid. His abdomen was tapped twice within the last ten days and on both occasions the fluid withdrawn was turbid from the presence of pus cells. Toward the end he developed typical signs of acute general peritonitis and died in an extremely prostrated state, being also very intensely jaundiced at this time.

*Macroscopic Pathologic Examination*—At necropsy the peritoneal cavity contained a large amount of turbid fluid. The peritoneum was uniformly covered by a delicate fibrinous exudate and also generally thickened. The exudate was particularly purulent over the liver, in the pelvis and in the region of the sigmoid. The intestines were distended and edematous.

The spleen (weight 525 gm) was considerably enlarged, dark and firm. The kidneys (weight left 275 gm, right 285 gm) were slightly enlarged, congested and showed a slight degree of chronic nephritis.

The pancreas was atrophic and there was also a mild degree of interstitial pancreatitis.

The heart (weight 350 gm) was atrophied and dilated in all its chambers but showed no interstitial myocarditis. The aorta and larger vessels were well preserved.

The gall-bladder was small and contained a little watery brown bile. The glands along the bile duct were slightly enlarged and considerably jaundiced.

The liver weighed only 700 gm and measured 25 cm laterally, 5 cm in thickness. Its surface for the most part was pinkish and smooth, but over the upper part of the right lobe and the under surface on both sides, near the hilum and also in the Spiegelian lobe were numerous elevated brown nodules. These nodules varied in size from that of a millet seed to 1 cm in diameter. On section the liver-tissue seemed to be almost entirely replaced by dense fibrous tissue. In the central portion of the organ in particular, there seemed to be almost no

liver-tissue remaining (Fig 1) The larger vessels of the liver showed no special gross exchange nor were there any evidences of thrombosis The islets of liver tissue were brown, well defined but somewhat irregular in outline They varied in size up to several which reached 2 cm in diameter These islets appeared quite homogeneous in character, although the larger ones were intersected by a delicate fibrous stroma They had lost the characteristic lobular markings

*Microscopic Pathologic Examination*—The brown areas were composed of liver-cells which for the most part were crowded together and had lost their trabecular and lobular arrangement These liver cells were also somewhat irregular in size, many being very large and hypertrophic, and some were noticed to contain several nuclei In this particular case, the process was of such long duration that signs of active liver-cell multiplication were wanting No mitoses were observed, although some evidences of amitotic nuclear division could be noted Yet the irregularity of the liver cells, and particularly their large size, indicated that some hyperplasia had occurred previously Contraction of fibrous tissue round islets of liver cells does not, as a rule, produce the appearances of compression which are common around tumors and in congenital syphilitic cirrhosis, and certainly is not responsible for the appearances described as due to liver cell hyperplasia These nodules of liver cell hyperplasia were comparatively small, but in some cases they tend to assume very large dimensions Two such cases I have seen diagnosed and operated on as abdominal tumor growths (In this connection, Barbacci<sup>2</sup> reports an interesting case of subacute atrophy in a woman whose liver was extensively cirrhotic and showed a tumor, composed of hyperplastic liver cells the size of a fetal head projecting on the right lobe, and another the size of a Tangerine orange on the surface of the left lobe)

In this case the fibrous tissue was very dense but contained only a small proportion of elastic tissue Included in this, there were numerous small islets of closely packed liver cells which apparently had escaped destruction and had proliferated considerably Bile ducts were fairly numerous, but in certain areas none were obvious at all Many of these ducts communicated directly with the liver cells, and others also could be traced to old persisting interlobular bile ducts

By serial sections, the course of the "ducts" could be traced more satisfactorily For the most part they pursued a definite course between liver cells with which they were directly continuous and some definite interlobular bile duct Many of these "ducts" connected with the liver-cells or interlobular bile ducts ended blindly, but they mostly formed part of an extremely interlacing network This network, which could be reconstructed from serial sections, seemed to be very similar in general distribution to the normal drainage system of the liver (compare Fig 2) although naturally considerably distorted by the inflammatory tissue through which the ducts extended When the complexity of anastomosis and accuracy of relationships of this reconstructed system was considered, it was apparently impossible that either liver cells or bile ducts could have produced these structures by proliferation

Evidences of proliferation of liver-cells in those areas which have survived are common in all destructive processes of the liver and are particularly marked in the extensive lesions of acute and subacute atrophy and in all the forms of cirrhosis In these areas, the multiplication and hypertrophy of liver-cells corresponds to the appearance which can be induced by experimental removal of large quantities of the hepatic tissue<sup>3</sup> As in experimental cases, the multiplication of liver-cells is much more frequently produced by a process of amitosis than by karyokinesis, which seems to occur as a relatively early phase in the process of liver-cell multi-

<sup>2</sup> Barbacci Beitr z path Anat u z allg Path, 1901, xxx, 45

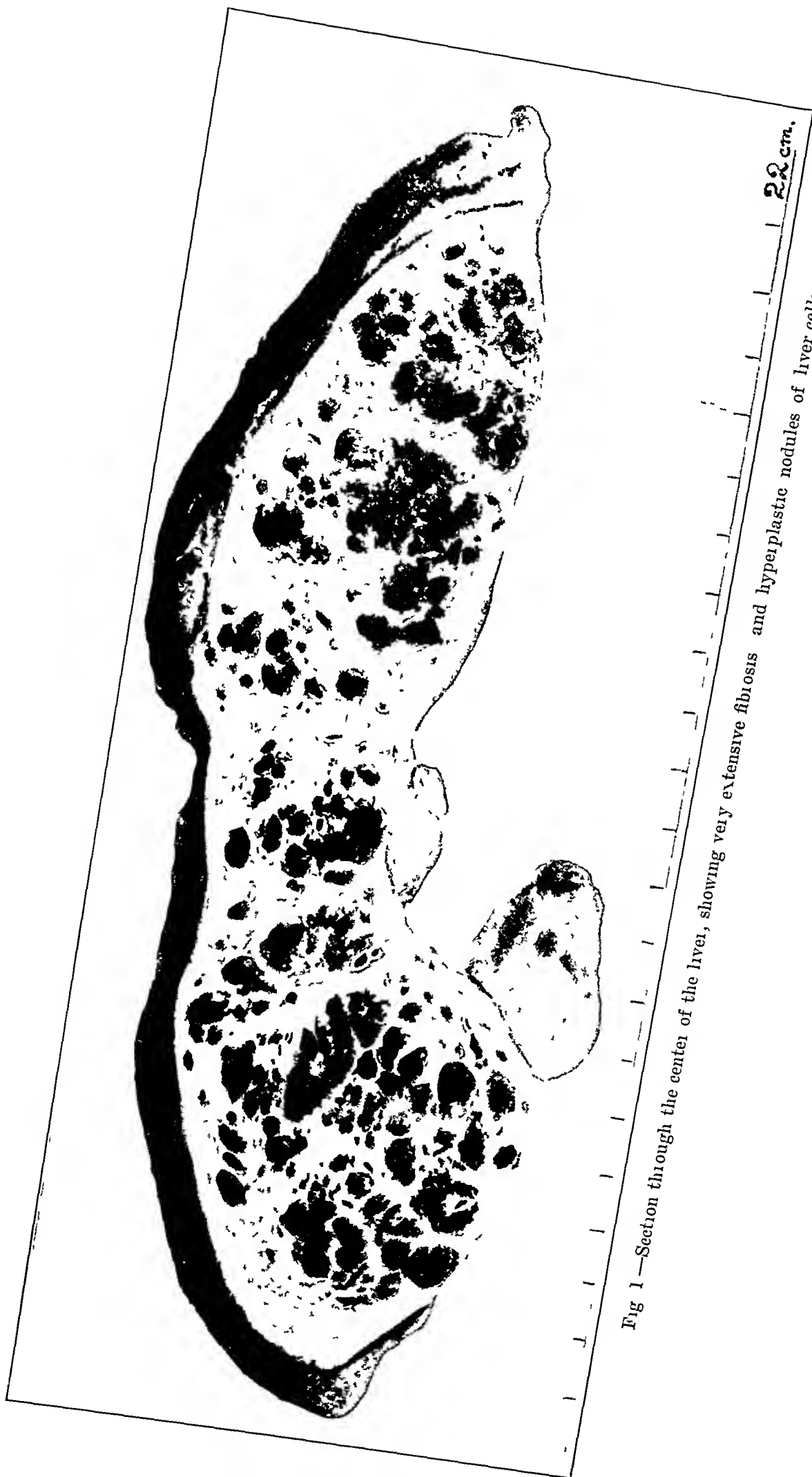


Fig 1—Section through the center of the liver, showing very extensive fibrosis and hyperplastic nodules of liver cells

plication Mitotic figures in the liver-cells are common in many degenerative and necrotic conditions of the liver. I have seen them in enormous quantities in a case of lymphadenoma. Yet in the same cases, coincident with the karyokinetic process, amitotic cell division is also taking place and in the later stages of repair seems almost entirely to predominate.

Although connections with "ducts" are common in such cases and evidences of liver-cell hyperplasia very marked, yet definite appearances suggesting a proliferation of these "ducts" from liver-cells are altogether wanting. The "ducts" so commonly found in new inflammatory tissue in the liver are also commonly directly connected with interlobular bile-ducts. As in the case of the liver-cells, no definite proof can be observed that the new "duct structures" are proliferated outward from some pre-existing interlobular bile-duct.

Catarrhal proliferative changes are common in the lining epithelium of the bile-ducts, both large and small, in almost all acute conditions affecting the liver, and can be induced experimentally by injection of the bile-ducts, or by inoculation of many toxic substances which seem to act chiefly by their irritative or destructive action in course of elimination down the bile-passages. The bile-duct epithelium, indeed, seems to have a very remarkable capacity for repair, as was shown by Serafini, who studied the regenerative capacity of the gall-bladder epithelium of guinea-pigs after its removal by a pad of cotton wool, the new cylinder epithelium being completely restored by the eighth day. This catarrhal proliferation does not, however, seem to have any tendency to induce sprouting from the ducts in the shape of the new "duct structures" so commonly found in inflammatory conditions of the liver.

Judging from the definite connections of these "ducts," their very definite and regular structural characteristics, and perhaps chiefly from their formation in a definite reticulum which more or less corresponds to the normal drainage liver system, it seems probable that they represent the normal surviving bile canaliculi connecting the liver-cells with the larger bile-ducts. In its new environment of inflammatory tissue, their epithelium from which the liver-cells have been denuded by necrosis, has become more cubical than the normal extremely flattened, almost invisible type. Analogies of this supposition are to be found in other organs, as for instance, the lining epithelium of the air alveoli in chronic inflammatory conditions in the lung and also in Bowman's capsule in the kidney in various types of chronic nephritis.

In the above-described case of subacute atrophy, there were several spots, and particularly one large area, where this idea could be somewhat substantiated. In these places there was an adenomatous arrangement of ducts (Fig. 3). For the most part, the duct spaces were continuous, widely dilated and in part, or altogether, lined by a cubical epithelium.



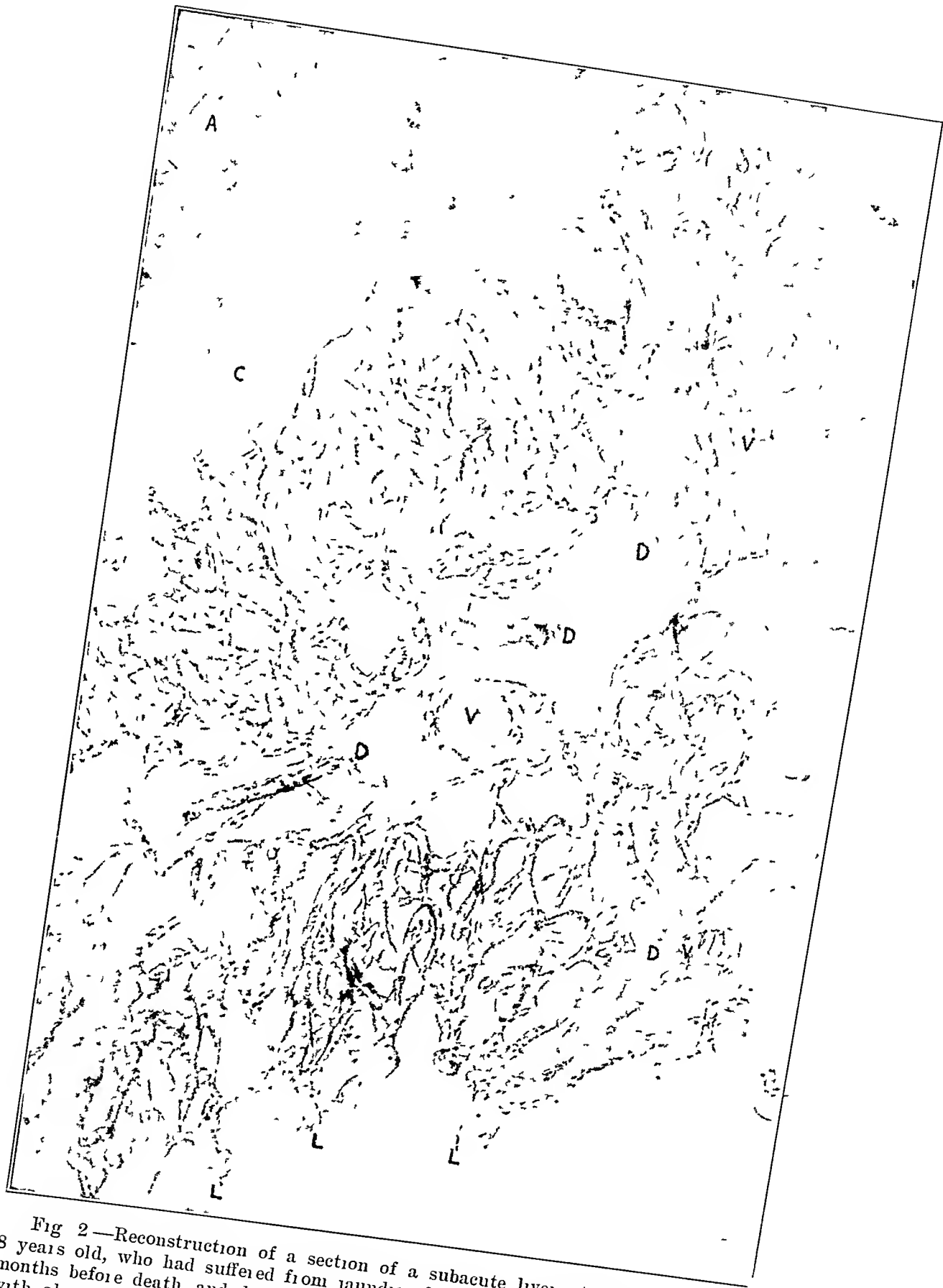


Fig 2—Reconstruction of a section of a subacute liver atrophy in a child 8 years old, who had suffered from jaundice for two months, commencing seven months before death, and during the last month slight jaundice had reappeared with also some ascites. This represents twelve sections each 10 microns thick. A certain spot in each was photographed, the positive plates of these superimposed, and a photograph taken of the whole. All the structures can be seen to have very definite relationships. V, V' and V'' are portal veins. D, D' and D'' represent interlobular bile ducts, L, Liver cells. An intricate ramifying system of ducts, connects the liver cells with the interlobular bile ducts, but many of the ducts also end blindly, where the liver cells with which they should connect become destroyed. A represents the system surrounding an adjacent portal tract. The liver cells between these two systems have disappeared and the two portal tracts with the surrounding inflammatory zones have become contiguous. In only a few situations as at C, do the two groups anastomose.

Many, however, were lined by an extremely attenuated type of cell and in parts a thin line of protoplasm containing no nuclei, alone formed the lining of the space. In several spots at the margins of these areas columns of liver-cells were directly continuous with this adenomatous formation. It was a question whether these liver-cells were evolved as a metamorphosis or proliferation from the "duct" structures or *vice versa*, but more probably they were only surviving liver-cells maintaining connections with their original bile-discharging system which for some reason, obstructive possibly, had become distended.

Subacute atrophy, then, may be considered as a more protracted stage of the acute condition when the subject has been more resistant and the destructive process less extensive. There may thus be types of every



Fig. 3—Area showing numerous adenomatous bile ducts. The lining of the spaces is in some partly cubical and in others very attenuated. Toward one corner is a patch of somewhat hyperplastic liver cells.

intervening stage between acute yellow atrophy and prolonged subacute cases, while complete recovery is also possible. Indeed, such cases of chronic atrophy may be recognized only when a certain failure of hepatic compensation is induced by some intercurrent condition. As a result, the prognosis of any disease in a case in which there has previously been any prolonged jaundice is necessarily guarded, as the vitality of such an individual with a reduced hepatic reserve is naturally diminished. The disease, in both the acute and subacute forms, almost invariably has an insidious onset unless it supervenes on some other preexisting condition. The whole aspect of the case is different from what is found in ordinary

cirrhosis The subject may complain of practically no other symptom or sign, except jaundice and, perhaps, some slight diffuse epigastric pain Gastro-intestinal troubles apparently are not the rule

As the process becomes more chronic and the regeneration of liver tissue and replacement fibrosis more extensive, the development of ascites is only natural In several of the more chronic cases which occurred in this institute, ascites has developed in about six months after the onset of the jaundice Such cases differ from ordinary atrophic cirrhosis only by having none of the toxic appearances or marked enlargement of the spleen as is the rule in cirrhosis

Acute atrophy, then, bears a certain relationship to all the forms of cirrhosis, and the substance which causes the original liver necrosis may be exactly the same, only varying in intensity and in rapidity of action Where a poison, derived either from bacteria or from some metabolic product from the intestine, acts on the liver for a short duration and is comparatively mild in toxicity, it causes a destruction of the hepatic tissues toward the periphery of each lobule which may be completely repaired by the remarkable regenerative capacity of the liver-cells, if, however, the destruction be too extensive, it is replaced by connective tissue, and a picture of a monolobular cirrhosis is produced Such livers are often large, commonly fatty, frequently presenting a smooth surface, and represent what used to be termed "biliary" or "Hanot's" cirrhosis Should the destructive change be more continuously applied, however, frequently destroying small sections of the liver and, in direct ratio, inducing replacement fibrosis and regenerative activity of the liver-cells, atrophic cirrhosis is produced In this form, a complete reconstruction of the liver results The terms "multilobular" or "portal" have been applied to it, but obviously are not correctly descriptive A continuous or frequently repeated reduction of liver substance, in spite of the great regenerative activity of the liver, eventually reaches a point where insufficiency occurs and the patient succumbs to jaundice The rearrangement of the liver from necrosis, replacement fibrosis and liver-cell hyperplasia, causes a tortuosity and variation in length and caliber of the blood capillaries which naturally increases the resistance to the portal circulation which may be sufficient to cause ascites It is, however, easy to see that a slowly progressing liver destruction may continue into an advanced cirrhosis without any jaundice, while only in the latter stages of the disease is ascites manifested, and only after a large amount of liver tissue has been destroyed or some intercurrent disease has developed does jaundice become evident

In conclusion, one can trace a direct connection between acute atrophy, subacute atrophy and cirrhosis of the liver in all its types, the difference in each depending on the extent and rapidity of accomplishment of the destruction of the liver

# THE DIAGNOSTIC VALUE OF MITOTIC FIGURES IN THE CELLS OF SEROUS EXUDATES

L. F. WARREN, M.D.

ANN ARBOR, MICH.

Since Quincke's<sup>1</sup> report in 1882, repeated attempts have been made to establish a diagnosis of malignant disease from the character of the cells present in pleuritic or peritoneal exudates. Where bits of tissue are withdrawn by the exploring needle, such a diagnosis may sometimes be made with a fair degree of certainty just as it has been made in the case of tissue obtained in stomach washings, the urine, the feces, etc. The recognition of isolated cancer cells, on the other hand, is extremely uncertain, and in 1900 Widal and Rivaut,<sup>2</sup> after a study of the cells in 600 exudates, concluded that it is difficult to diagnose cancer from such cells, on account of their general resemblance to endothelial cells. In one of the cases to be reported, the presence of many mitotic figures rendered the diagnosis of malignancy almost certain, in the second case their appearance in small numbers strengthened a similar diagnosis, and in the third case they changed a probable diagnosis of sepsis to one of malignancy. A review of the literature shows how few cases have been reported in which large numbers of mitotic figures were found in the cells of serous exudation. We shall therefore report these three cases and review the literature with the object of ascertaining how much reliance may be placed on such findings in establishing a diagnosis of malignant disease.

## REPORT OF CASES

**CASE 1—Patient**—E. T., male, 14 years old, was admitted to the University Hospital March 25, 1910, complaining of swollen abdomen. The family and past history were negative. About Dec. 11, 1909, the patient first noticed sharp pains across the lower abdomen. These recurred at irregular intervals but he did not go to a physician until December 21. In January his abdomen began to swell and he experienced dull pains after eating. Although his appetite remained good he suffered at times from nausea and vomiting. The bowels were loose. Occasionally his feet were slightly swollen. He had a slight cough with a little expectoration. On March 17 six quarts of fluid were removed from his abdomen and on March 24 three quarts more were obtained.

**Examination**—The patient was an emaciated, frail boy. In the right clavicular region there was a mass of ten or twelve glands varying from the size of a pea to that of a hickory nut. These were freely movable and not tender. Above

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\*From the Department of Internal Medicine, University of Michigan.

1 Quincke H. Ueber die geformten Bestandtheile von Transsudaten. Deutsch Arch f klin Med, 1882, xxx, 580.

2 Widal and Rivaut. De l'étude histologique des épanchements séro-fibrineux de la plèvre, Compt rend Soc de biol, 1900, lvi, 648.

the left clavicle two enlarged glands could be felt, but no other glands were palpable. The lower portion of the chest posteriorly showed dulness with diminished fremitus and breath sounds. The tensely swollen abdomen caused a bulging of the lower ribs, the veins over the sides of the abdomen and chest were dilated



Fig 1—Monaster

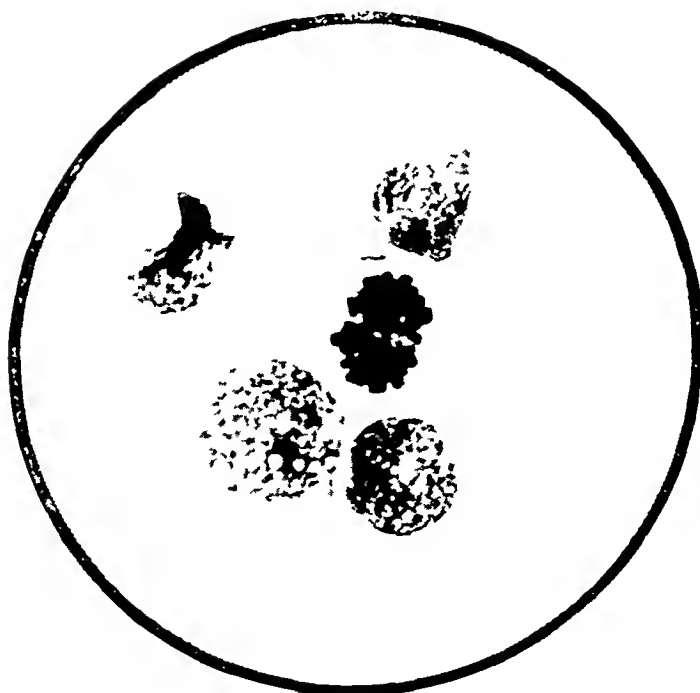


Fig 2—Beginning diastel

Typical signs of fluid in the abdominal cavity were obtained and on palpation an indefinite and deeply situated tumor mass could be felt just above the umbilicus. On March 27, two days after admission, 1,300 cc of fluid were removed

from the abdomen. Following the tapping, the tumor could be felt somewhat more distinctly as a transverse mass just to the left of the umbilicus. This was hard and irregular, was firmly fixed and was not tender. Rectal examination showed that it extended into the pelvis in front of the rectum. During his stay

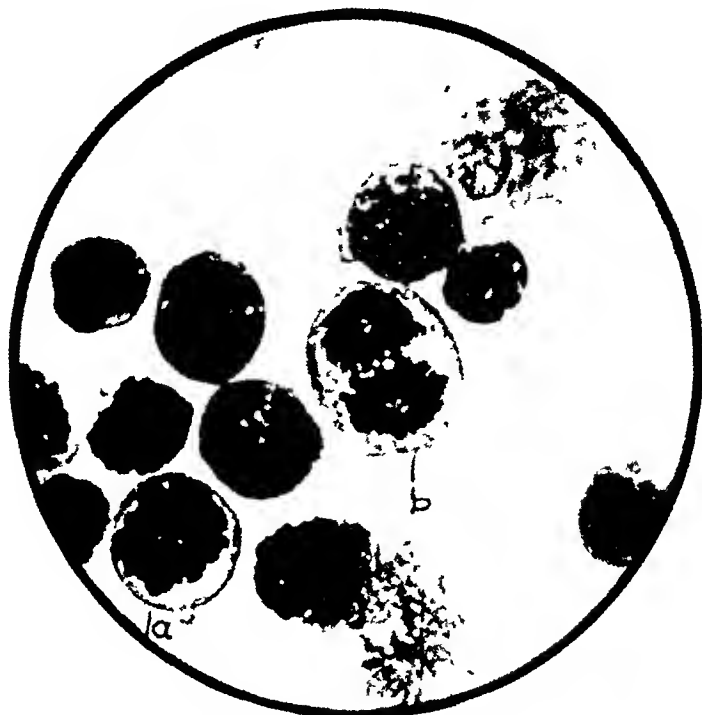


Fig 3—Resting tumor cell (a), diastol (b)



Fig 4—Diastol—later stages

in the hospital his temperature showed a daily fluctuation from about 98 to 100 F. The urinary examination was negative except for the presence of a few granules and hyaline casts and, on one occasion, a blood cast. The stools showed a positive

occult test for blood with a slightly increased number of muscle fibers. The blood-pressure was normal. The blood examination showed 3,000,000 red cells, 8,000 leukocytes and 55 per cent hemoglobin. A differential count of the leuko-

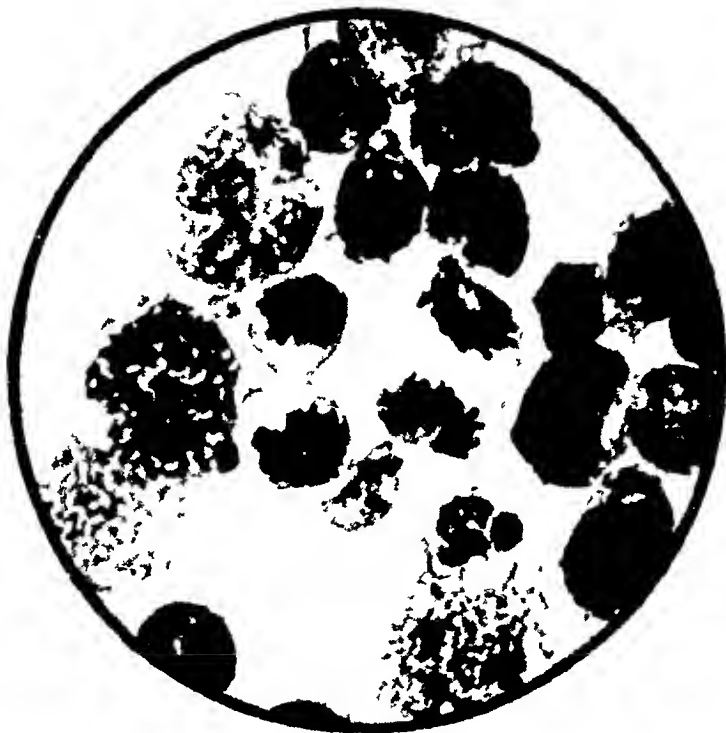


Fig 5—Diaster—later stages

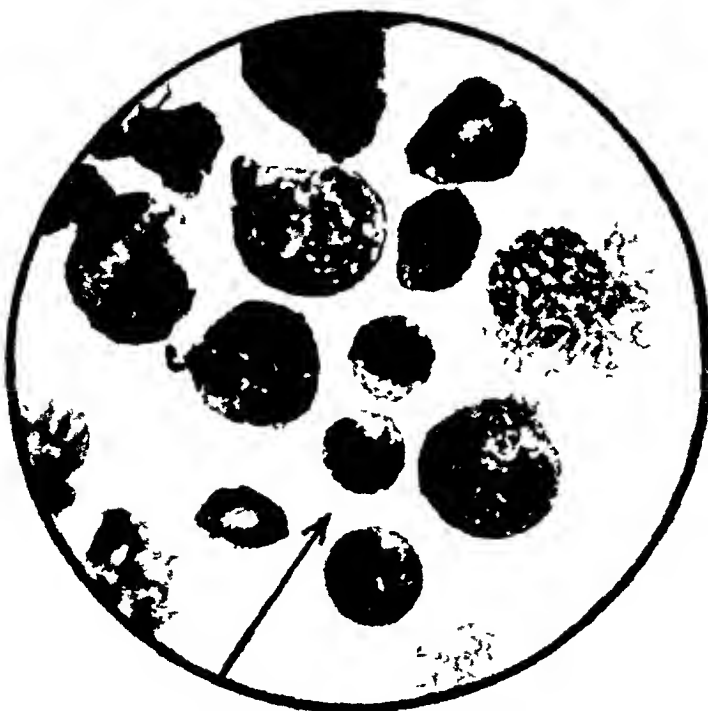


Fig 6—Arrow points toward two new tumor cells

cytes showed 24.4 per cent mononuclear cells, 71.4 per cent polynuclear, 0.7 per cent eosinophilic mononuclears and 3.5 per cent degenerates. The fluid obtained from the peritoneal cavity showed the following characteristics: specific

gravity, 1.010, large amounts of albumin (one half volume by heat and nitric acid test 15 gm per liter by Esbaeh), very heavy test for nucleo albumin, tests for mucin, sugar and bile negative. It contained 17,320 white cells per cmm. A differential count of these showed 37 per cent typical small lymphocytes, 51 per cent atypical mononuclear cells and 12 per cent polymuclear. Eight red cells were noted in counting 200 white cells. Every field of prepared films showed tumor cells in both resting and division stages. The former could be told from the lymphocytes (1) by their size, they being from 16 to 24 microns in diameter, (2) from the nucleus, which did not stain as heavily and gave the appearance of being fissured or slightly lobulated, (3) the protoplasm was increased in amount over that of the lymphocytes and most frequently showed small areas of vacuolization. Of the division figures, the monasters (Fig 1) were the most plentiful, but there were all stages passing from same down through the equatorial plate arrangement to the typical diaster (Figs 2 and 3). Cells showing beginning constriction of the protoplasm (Figs 4 and 5), as well as new tumor cells ready to separate (Fig 6), were fairly abundant. The figures here pictured were all taken from the preceding case, about one cell in twenty five showed some form of division.

*Course*—The patient rapidly failed after coming into the hospital and died on April 1, of exhaustion. At first he was suspected to have a peritoneal tuberculosis but the absence of a Pirquet reaction, the failure to find tubercle bacilli in the peritoneal fluid and in the stools, and the large number of mitotic figures in the cells of the ascitic fluid changed the clinical diagnosis to a neoplasm involving the peritoneal cavity.

*Pathology*—At necropsy, performed by Dr Warthin, on April 1, 1910, the whole abdomen was found to be filled with a soft, nodular mass which proved to consist mainly of tumor of the omentum. The coils of the intestines were covered with a fibinous exudate. Tumor nodules were present in the mesentery, intestines, peritoneum and retroperitoneal glands and tissues. The diaphragm and the parietal pleura were studded with tumor masses. Nodules present on the lower surface of the right lung had apparently extended to it from the diseased diaphragm. The tumor had also involved the bronchial glands, the spleen, the kidneys, the liver and the bladder-wall. Microscopically it proved to be a lymphosarcoma. The origin of the tumor could not be determined.

*CASE 2—Patient*—W. B., aged 32, entered the University Hospital on Feb 21, 1910, complaining of abdominal enlargement. The family and past history were negative. The present trouble began six weeks before admission, when the patient first noticed that his abdomen was becoming swollen. On the following day he was suddenly taken with sharp, paroxysmal pains in the left lower abdomen, which radiated to the right side. Following this the abdomen grew rapidly in size and although the severe pains abated, he had distress after eating, became very weak and dyspneic, and lost about 20 pounds in weight.

*Examination*—The patient was a moderately emaciated man. The abdomen was very much distended, bulging somewhat more to the left than to the right. On account of the tension, palpation was difficult but in the left flank a hard mass could be indistinctly felt. February 22, the abdomen was tapped and 6 liters of a brownish, slightly turbid fluid were removed. Following this a nodular mass could be felt, extending from somewhat above the umbilicus down to Poupart's ligament on either side. This was hard, rather nodular, and but slightly movable. Rectal examination showed that the mass extended into the pelvis in front of the rectum.

*Course*—The fluid collected rather rapidly after the tapping and respirations became increasingly more difficult. On March 2 the patient was again tapped and 7,700 cc of yellowish brown fluid obtained. Following this tapping, the fluid did not re collect so rapidly but the patient gradually became weaker, vomited considerably and died on March 14.



Numerous blood-counts showed a normal number of red blood corpuscles and a normal percentage of hemoglobin. The leukocytes were moderately increased, ranging from 10,500 to 15,000. No abnormalities in the appearance of a stained smear were noted. The urine was negative, the stools showed heavy tests for occult blood. The injection of 5 mg of tuberculin produced no reaction. An examination of the fluid recovered at the second tapping showed a specific gravity of 1.018 and large amounts of albumin, so that the tube boiled solid. The fluid contained 1,400 white cells and 240,000 red cells per c mm. The differential count of the whites gave 61 per cent lymphocytes, 7 per cent polynuclears, and 32 per cent large mononuclear cells. A small number of mitotic figures were found. A clinical diagnosis was made of malignant tumor involving the omentum.

*Pathology*—At the necropsy, performed by Dr Warthin, March 16, 1910, the omentum was found greatly thickened and nodular, forming a thick apron reaching to the pelvis. Fifteen hundred cc of fluid of an opalescent, sticky character were found in the left pleural cavity. A smaller amount of fluid was present on the right side. The parietal pleura showed numerous minute tumor granules, with some nodules on the visceral pleura. The peritoneum was thickened and edematous and was covered with a fibrinous exudate. At the pylorus was found an irregular ulcer,  $2\frac{1}{2}$  inches in diameter, with slightly elevated borders. Opposite the ulcer there was a nodular mass of tumor tissue. The smaller intestines were encased in a layer made up of tumor tissue and fibrin. Lymphatics in the lesser curvature of the stomach were enlarged and nodular. Several tumor nodules were present in the liver. On section, the tumor proved to be a colloid carcinoma, in places of the adeno type, in other places rather scirrhous. The cancer showed marked mucoid degeneration.

*CASE 3—Patient*—Miss R, seen by Dr Hewlett in consultation with Dr Gates of Ann Arbor, on August 22, 1911, complaining of weakness, also emaciation and fever. Family history negative. Past history negative up to about one year ago at which time a multilocular cyst of the ovary was removed by Dr Darling. Subsequently she had a stitch abscess but recovery was otherwise perfect. About July 4, 1911, she noticed a pain in the left foot, and a week or so later a pain in the right side. She had lost weight and strength almost continually since that time. She had noticed no chills or sweats but her temperature for the past few days had ranged between 100 and 101 F. She had had a succession of reddish spots appear under the skin which were painless, not tender, and gradually faded. She had coughed considerably especially when she raised mucus.

*Examination*—Patient appeared seriously ill. The skin was sallow and there was some dyspnea. At the base of the left chest behind there were numerous crackling râles. At the right base there were signs of fluid extending to the sixth or seventh spine behind, well up into the axilla, and to about the fourth intercostal space in front. Beneath the skin in various parts of the body were a number of spots which were reddish, slightly elevated and from 2 to 3 cm in diameter. The older ones faded to a yellowish color. The blood showed no marked anemia. There were 17,000 leukocytes. The stomach analyses had shown little or no free hydrochloric acid. The sputum was negative for tubercle bacilli on several examinations. The fluid aspirated from the right chest and was bloody in appearance. Smears of the centrifugized material showed a great many red cells, most of which are either broken or cremated. The polynuclears have a predominance over the mononuclears, they making up 82 per cent of the differential blood-count. In addition to these cells already mentioned are large numbers of balls of cells, similar to those described and pictured by Quincke. The nuclei in these cells stain poorly and the protoplasm of many show fatty degeneration. They vary in size from 30 to 50 microns in diameter and some of the cellular groups have a diameter of 100 microns. With the Wright stain the nuclei in these groups are placed at the periphery while the center stains rather palely. In both the single cells and cell masses are found division figures. Most of these are in the monaster or beginning diaster stage.

*Diagnosis*—Previous to the aspiration of the fluid from the right chest, and under the impression that the ovarian tumor had been benign, a tentative diagnosis of sepsis was made based on the fever, leukocytosis, effusion and subcutaneous spots. Later it seemed much more probable, however, that we were dealing with a malignant disease of the pleural cavity, in view of the character of the exudate and subsequent examination of sections of the tumor. The latter were examined by Dr Warthin, who reported a papilliferous cystadenoma with layers of necrosis and areas of active cell proliferation almost solid. He expressed the opinion that the tumor was malignant.

*Course*—The patient failed rapidly and died Aug 27, 1911. No autopsy was obtained.

#### REVIEW OF LITERATURE

To ascertain the diagnostic value of mitotic figures in serous exudates one must consider their frequency in malignant as well as in non-malignant conditions. Reider<sup>3</sup> first described such figures in an exudate due to malignant new growth. In his case both ascitic and pleural fluids showed many division figures of mitotic as well as of amitotic nature and at post mortem a sarcoma (carcinoma?), probably beginning in the ovary, was found. In 1897 Dock<sup>4</sup> reported a case of carcinoma of the stomach undergoing colloid change, in which many cells of the ascitic fluid showed mitotic figures. In the same article he mentions a pleuritic exudate secondary to carcinoma of the breast where a few mitoses could be found. In the same year Warthin<sup>5</sup> reported a spindle-celled sarcoma invading the pleural cavity. The pleuritic exudate showed typical small spindle cells, with numerous division figures. Turton,<sup>6</sup> in 1905, mentioned a case in which the fluid from the right side of the chest showed "large sarcoma cells with mitotic nuclei," the diagnosis being confirmed at autopsy. Mitotic figures in the spinal fluid have been described by Vidal and Abrami,<sup>7</sup> and by Facchini<sup>8</sup> in cases of sarcoma involving the meninges. Marini and Fiorini<sup>9</sup> reported four cases of carcinoma with effusions and claimed to have found division figures in each. Their microphotographs, however, are not convincing. Their figures showed

3 Reider, G. Zur Diagnose der "Neubildung" bei klinische mikroskopischen Untersuchungen von Transsudaten, *Deutsch Arch f klin Med*, 1895, liv, 544.

4 Dock, G. Cancer of Stomach in Early Life and the Value of Cells in Effusions in the Diagnosis of Cancer of the Serous Membrane, *Am Jour Med Sc*, 1897, cxiii, 655.

5 Warthin, A. S. The Diagnosis of Primary Sarcoma of the Pleura from the Cells Found in the Pleuritic Exudate, *Med News*, 1897, lxxi, 489.

6 Turton, E. The Cytodiagnosis of Pleural and Cerebrospinal Fluids, *Practitioner*, London, 1905, lxxiv, 497.

7 Vidal, F., and Abrami, P. Cytodiagnostic du cancer des centres nerveux. Présence de cellules néoplastiques dans le liquide céphalo rachidien endocardite végétante cancéreuse, *Rev Neurol*, 1909, xvi, 75.

8 Facchini, G. Un caso di sarcomatosi diffusa metastatica della pia meninge cerebrale e spinale con caratteristico reperto citodiagnostica del liquido cefalo rachidiano, *Polichinico*, Rome, 1908, xv, 977.

9 Marini, D. G., and Fiorini, M. Valore dell' esame istologico dei liquidi ascitici nella diagnosi della neoplasie peritoneali, *Riforma Med*, 1908, xxiv, 1.

cells with several separate nuclear masses but without mitotic skeins. Such cells are found in a great many effusions other than malignant ones. In spite of a careful search of the literature, the above were the only cases discovered in which exudates due to malignant disease showed free cells undergoing mitotic division. It is probable, of course, that others have been observed and that a few reports have been overlooked. Raubitschek<sup>10</sup> has expressed the opinion that division figures, typical or atypical, indicate the neoplastic nature of the exudate with a probability bordering on certainty.

On the other hand, numerous effusions complicating malignant disease have been reported in which division figures were not described. Seven such were reported by Ross,<sup>11</sup> six by Schlesinger,<sup>12</sup> five by Barjon and Cade,<sup>13</sup> two by Gwyn,<sup>14</sup> three by Miller,<sup>15</sup> one by Vickery, Wright and Richardson,<sup>16</sup> one by Miller and Wynn,<sup>17</sup> two by Beneke,<sup>18</sup> and one by Guiland.<sup>19</sup> Labbé, DeLillie and Aguinet<sup>20</sup> report a case of sarcoma of the pleura in which they recognized sarcoma cells but were unable to find division figures. Nattau and Larrier<sup>21</sup> also recognized cancer cells in cases of cancerous pleurisy but were unable to find divisions. In two cases of malignancy during the past year we were unable to find division figures. In many of the above cases division figures were expressly looked for while in others no mention was made of their absence. Malignant disease may cause exudates by a mechanical obstruction of the veins or lymphatics or by exciting a low-grade inflammation. In many of these cases, how-

10 Raubitschek, H. Die cytologie der Ex- und Transsudate, *Centralbl f d Grenzgeb d Med u Chir*, 1906, ix, 337.

11 Ross, E. A. A Study of Cytodiagnosis with Especial Reference to Its Application in Clinical Medicine, *Tr Path Soc London*, 1906, lvii, 361.

12 Schlesinger. Ueber das Auftreten von Mononucleose in Pleura exudation bei Lungen- und Pleuratumoren, *Wien Gesellsch f inn Med u Kinderh*, 1909, xii, 960.

13 Barjon, F., and Cadé, A. Eosinophilie pleurale, *Arch gén de méd*, 1903, cxvii, 1859.

14 Gwyn, N. Carcinoma of Abdominal Cavity. Puncture of Intestine During Paracentesis Abdominis, *Am Jour Med Sc*, 1904, cxxvii, 592.

15 Miller, J. Transudates and Exudates with Report on Seventy-Five Fluids, *Am Med*, 1904, viii, 835.

16 Vickery, H. F., and Richardson, O. Malignant Disease of Pleura, *Boston Med and Surg Jour*, 1907, clvii, 824.

17 Miller, J., and Wynn, W. H. A Malignant Tumor Arising from Endothelium of the Peritoneum and Producing a Mucoid Ascitic Fluid, *Jour Path and Bacteriol*, 1908, xii, 267.

18 Beneke. Ueber freies Wachstum metastatischer Geschwulstelemente in serösen Hohlen, *Arch f klin Med*, 1899, lxiv, 237.

19 Guiland, G. L. Cytodiagnosis of Pleural Effusions, *Scot Med and Surg Jour*, 1902, x, 490.

20 Labbé, Delillie and Aguinet. Cytodiagnostic de la pleurésie sarcomateuse, *Bull Soc d'anat de Paris*, 1902, Serie VI, iv, 507.

21 Nattau and Larrier. Cytologie des pleurésies cancéreuses, *Compt rend Soc de biol*, 1905, p 709.

ever, tumor tissue involved the serous membranes and not a few authors regarded the cells present in the effusion as tumor cells. We have already mentioned the difficulty of recognizing free-growing tumor-cells in serous exudates. In Beneke's third case, however, the cells showed pigment similar to that in the parent melanosarcoma and there was little doubt about their nature. In the great majority of cases, therefore, mitotic figures have not been found in the exudates accompanying malignant disease. Occasionally, however, they occur in such number as to form the most striking feature of the cell-count.

There remains for consideration the occurrence of mitotic figures in the cells of exudates due to other causes than malignancy. Personal experience as well as a review of the literature indicate that mitotic figures are extremely rare in such exudates. Only two instances have been encountered in literature. One was reported by Dock in a pleurisy following the removal of a diseased appendix. This was probably of an infectious character as was shown by the large number of pus-cells and the presence of streptococci. The other was reported by Ross, in a patient whose clinical history suggested tuberculosis and who was in satisfactory condition eleven months after the tapping. In Dock's case the number of mitotic figures was not very great, in Ross' they were said to be numerous, and it is to be regretted that more data concerning this case are not available. The extreme rarity of mitotic figures in non-malignant effusions is now well established, for the active interest in cytodagnosis during the past few years would certainly have brought to light more cases had they existed. It is probable, as Dock has said, that "the difference between malignant and non-malignant exudates in this regard is of degree rather than of kind." Where great numbers of figures are found, the diagnosis of malignancy is almost certain while, where few are present, the diagnosis is suggested but not certain.

The cases showing numerous, actively-dividing cells, free in the fluid have occurred most frequently in cases of sarcoma. In Dock's case, however, the diagnosis was colloid carcinoma. Beneke has described a case of carcinoma involving the pleural cavity in which balls of free-growing, unattached tumor-tissue were found in the pleural cavity. The cells in these balls frequently showed mitotic figures. In two cases of sarcoma, on the other hand, he found free, individual cells which he regarded as tumor-cells. He is inclined to explain the difference by assuming that in carcinoma new stroma was formed which held the cells together, while in sarcoma this was lacking and the cells appeared free in the fluid. When many mitotic figures are present the tumor-cells are proliferating actively in the body-fluids. The condition may be of some biological interest in connection with the fact that tumor-cells have recently been cultivated outside of the body. Their free growth in a serous exudate

# MALIGNANT EFFUSIONS WITH MITOTIC FIGURES

Author	Date	Age Yrs	Character of Tumor	Site of Tumor	Differential Count, Etc
Rieder	1895		Sarcoma (caichnoma ?)	Prim ovary, sec peritoneum, pleura, etc	Cells vary in size and shape, great variation in the nuclei, many mitotic figures
Dock	1897	20	Cancer	Prim stomach, sec peritoneum	Many mitoses so that every contains one or more
	1897	50	Carcinoma	Prim breast, sec pleura	Excessive red-cells and lymphocytes, many mononuclear and few endothelial cells, very few showed mitoses—two to two in each preparation
Waithin	1897	47	Sarcoma	Prim pleura	Many typical spindle cells, singly and in groups, numerous mitoses of symmetrical character
Turton	1905	23	Sarcoma	Pleura	"Large sarcoma cells with mitotic nuclei"
Widal and Abrami	1908	47	Carcinoma	Prim stomach, sec internal capsule	Cells gave glycogenic reaction
Facchini	1909		Sarcoma	Prim —, sec meninges	Neoplastic cells with mitosis
Warren	1911	14	Lymphosarcoma	Prim mesenterly and intestines, sec peritoneal cavity	37 per cent lymphocytes, 51 per cent atypical mononuclears, 12 per cent polynuclears, very numerous mitoses
	1911	32	Colloid carcinoma	Prim stomach, sec peritoneum	61 per cent lymphocytes, 7 per cent polynuclears, 32 per cent large mononuclears, many red-cells, very few mitoses
	1911	48	Papilliferous cystadenoma	Prim ovary, supposed sec pleura	80 per cent polys, great many red cells, many balls of cells, numerous mitoses

would seem to indicate that the body defenses have practically succumbed to the neoplasm

#### CONCLUSIONS

1 Very many cells undergoing mitotic division in serous exudates are almost diagnostic of malignant disease

2 This occurs more often in sarcoma than in carcinoma

3 A small number of mitotic figures is suggestive of malignant disease but is of no certain value in diagnosis

4 In the majority of the exudates associated with malignant disease no division figures are seen

I wish to thank Dr A M Barrett for the microphotographs which he so willingly made for me

## PERCUSSION SIGNS OF PERSISTENT OR ENLARGED THYMUS \*

THOMAS R. BOGGS, M.D.  
BALTIMORE

Although we know very little about the functions of the thymus, it has certain clinical associations which make it important, and closer observation may enlarge our knowledge of its relation to disease.

The gland occupies a position high in the superior mediastinum, lies close to the sternum and it is not covered by the lungs. Ordinarily the lobes are unequal, the left being the larger and longer, often extending as low as the fourth rib in infants. The gland is attached by one or two suspensory or thyrothymal ligaments to the lower poles of the corresponding thyroid lobes. Otherwise the thymus is but slightly bound to the surrounding tissues and is free to move in the direction of the long axis of the sternum. If it is borne in mind that the thyroid gland is in turn connected to the hyoid bone and from this to the mandible by more or less continuous ligaments and muscles, it is seen that a ligamentous chain extends from the anterior part of the lower jaw obliquely downward and backward to the thymus.

This connection is of interest in explaining the mechanics of the movable thymus dulness described below, for in retraction of the head, more tension is brought to bear on the structures anterior in the neck than those lying close to the vertebral column, and these structures move through a greater arc.

In the normal atrophic state of the adult thymus, the small amount of gland substance and areolar tissue is too thin to give any appreciable dulness on percussion over the manubrium, or just to the left of the sternal margin. But if, for any reason, the gland has not atrophied or has become enlarged, then there is a dulness easily determined on medium percussion over the manubrium and in the first and second left interspaces more rarely in the third interspace. In many cases, also, this dulness is perceptible to the right of the sternum in the first interspace, less frequently in the second.

The differentiation of dulness in the mediastinum due to thymus enlargement from other masses in this region will depend on several factors.

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\*Read at the twenty sixth annual meeting of the Association of American Physicians, Atlantic City, May 9-11, 1911.

1 The thymus is higher and more superficial than the mediastinal lymph-glands usually involved in tuberculous or other mediastinitis, or which may be the seat of primary or metastatic tumors. These lymphatics lie deep, near the hilum of the lung, and when diseased, are usually more or less fixed by adhesions to the surrounding tissues. It is further to be observed that thoracic aneurysms, tumors, or inflammatory masses of the mediastinum are practically fixed in position and no considerable change in percussion is made out, when the head is retracted.

2 Thymus dulness is almost constantly much more marked on the left of sternum than on the right.

3 Thymus dulness can be made to shift by the following maneuver, viz. The patient sits up, the back is supported by the nurse or assistant, if necessary. The chin is depressed toward the sternum. The dulness is outlined behind the manubrium and in the interspaces, then the head is retracted as far as possible toward the mid-line of the back and, on repeating the percussion, the lower border of dulness will be seen to have shifted upward, often as much as an interspace or more. On again depressing the chin, the dulness assumes its former position. In recognizing minor degrees of movement, it is advisable to keep the pleximeter fingers constantly in place, avoiding the slight movement of the skin by first pushing the skin up toward the neck before the retraction of the head puts it in tension.

Another point which may be noted here is the fact that in some cases of persistent or enlarged thymus, there may be no dulness in the first interspace, but only in the second and below it. In such instances, a shift in both upper and lower borders of dulness may be made out.

The material on which these deductions are based was derived from an orphan asylum for colored girls and from the wards of the Johns Hopkins Hospital and the City Hospital.

In the orphan asylum, sixty-six girls were examined during an epidemic of measles. Of these, fourteen had the disease or were convalescent. In age they were between 5 and 18 years, thirty-seven of them between 10 and 14 years. Of the sixty-six children, thirty-five showed positive signs of persistent or enlarged thymus. This number included twelve of the measles cases. All but three of the positive cases showed general lymphadenitis of varying grades, many had also hypertrophied tonsils.

Of the hospital patients, fourteen in number, nine were between 8 and 18 years, and five between 22 and 47 years. Of the fourteen patients, only five were colored. The children were nearly all sick with acute infections, including typhoid, pneumonia, pleuritis, diphtheria, etc. Of the adults, two had exophthalmic goiter and two diphtheria, though it is to be observed that these last have still the same signs of enlarged thymus, a year or more after the diphtheria. The extent of dulness varied from 2 to 7 cm. from the midsternal line, the average being about 2.5 to 3 cm.



Only two patients could be examined with Rontgen ray Both had very large glands and showed a shifting shadow in the thymus region to left of the manubrium

One case of the series came to autopsy, when the percussion findings were amply confirmed by the presence of a gland measuring 9 cm by 8 cm by 2 cm

In conclusion, it may be remarked that lymphatic hyperplasia seems to be more common in the black race, which may explain the high percentage of positive findings in the orphan asylum children

This method is put forward tentatively and for criticism, as it has not been noted in the literature on physical diagnosis

Special thanks are due to Drs C R Austrian and W L Estes for assistance in the study of the orphan asylum cases

21 West Chase Street

# NITROGEN AND FAT METABOLISM AND OTHER FUNCTIONAL TESTS IN A CASE OF CHRONIC PANCREATITIS

HENRY G BARBOUR, M D  
BALTIMORE

A case of chronic pancreatic insufficiency without diabetes will be reported here, with special reference to the metabolism of nitrogen and fat. A discussion of other functional tests of the pancreas is included. The patient was one of Dr L. F. Baiker's in the medical clinic of the Johns Hopkins Hospital. This report falls under three general heads (1) Clinical Course, (2) Metabolism Studies, (3) Other Functional Tests.

## CLINICAL COURSE

*Patient*—Med No 24917 W P R, aged 34, attorney. Admitted Nov 20, 1909, complaining of indigestion and diarrhea. The following history was obtained at that time.

*Family History*—Negative. A long-lived healthy family.

*Personal History*—He had had the usual diseases of childhood, and diarrhea of varying severity from the age of 3 to 13 years, malaria at 22, "eczema" with painful pruritus of arms, legs and back, from the age of 25 to 30 years. There were occasional attacks of sharp pain in abdomen during greater part of life. Alcoholic and venereal history were negative.

*Present Illness*—Began September, 1908, with nocturnal attacks of severe pain in epigastrium. Occurrence every three or four nights, gradually increasing in frequency until occurring every night. Entered a hospital in North Carolina Nov 19, 1908, with diagnosis of cholecystitis.

*Operation*—Nov 24, 1908. Pus was found in gall-bladder and about 75 gallstones were removed ranging in size from a wheat grain to a pea. A few were found in the hepatic duct and one in the common duct. No bile in stools at time of operation. Bile appeared first on the third day after operation. Left hospital after one month.

Jaundice, present previous to operation, persisted until March, 1909. A skin rash on head, arms, legs and lower abdomen in the form of red concentric rings appeared with pruritus at close of January, 1909, duration three weeks.

Patient has not had a formed stool since operation. Stools are said to have been for the most part pasty, yellow or clay colored. Feb 15, 1909, diarrhea began, with one to five stools a day, continuing to the present time. Marked loss of weight.

Patient was in a sanatorium from March 25 to May 15, 1909, with temporary anasarca. Since then unable to work except a small amount in September, 1909. Has had no abdominal pain since operation and gives no history of excessive salivation.

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\*From the Chemical Division of the Medical Clinic of the Johns Hopkins Hospital.

*Physical Examination*—A very much emaciated man, muscles markedly wasted. Extreme pallor of mucous membranes. Mind clear and active. Eyes, ears, throat, lungs and heart normal. Pulse, small volume, regular in force and rhythm, artery wall slightly sclerotic. Abdomen scaphoid, walls thin. Large operative scar in right upper quadrant. Liver edge slightly lower than normal. Spleen not palpable. Rectal examination negative. Reflexes normal.

*Urine*—Amber or orange color, slightly cloudy, specific gravity 1008-1020. Acid. No sediment. Sugar negative. Albumin 0.25 gm (Tsuchiya reagent). Microscopic examination negative. Bile +. Urobilin +. Indican negative. Cammidge reaction. No crystals were obtained from 50 cc. From 4 liters, large yellow sheaves soluble in dilute sulphuric acid were obtained with melting-point 130 F.

*Stools*—Macroscopic. Nov. 20, copious semi-solid, very fatty throughout, appearing like butter and giving the odor of butyric acid. Large quantities of undigested particles of meat, potatoes, etc. After November 22, dark brown, thick fluid, steatorrhea diminished or absent, still many undigested food particles. Stool sometimes showed oily layer over surface. Sublimate test for bile positive for urobilin, on one occasion showed bilinubin also. Occult blood test negative. Gross' casein test showed presence of trypsin. Schmidt's nuclei test showed few nuclei intact.

Microscopic. Neutral fat in amounts varying with macroscopic appearance. Large and small droplets staining red with Sudan III. Fatty acid crystals. Large numbers of striated muscle fibers, some showing nuclei intact. No parasites. No stones of any sort.

*Blood*—Fresh smears normal. R B C, 3,056,000. Later 4,000,000. W B C, 7,000. Hemoglobin (Sahli) 70 to 79 per cent.

*Stomach Contents*—Forty-five minutes after a Dock test breakfast (1 shredded wheat biscuit with 400 cc of water), 40 cc of fluid were recovered containing no free hydrochloric acid. Total acidity 4.0 "acidity per cent."

Patient's weight 100½ pounds.

*Subsequent Course*—Little change in condition during two weeks of metabolism studies. Weight varied as follows: November 28, 101 pounds, December 5, 97 pounds, December 10, 98½ pounds, December 13, 101 pounds, December 18, 103 pounds.

December 11, marked improvement began on light diet with pancreatin rhenania gr in p c and CaCO<sub>3</sub> gr in p c. Daily examination of urine, while in hospital, gave negative Fehling's tests without exception. Left hospital Dec. 27, 1909, weighing 120 pounds, including wearing apparel.

March 1, 1910. Patient began to have formed stools. April 1910, weighed 147 pounds. May 10, 1910, examination by Dr. Barker showed condition much improved, muscles growing rapidly. Patient works seven hours a day. Is taking 6 gr pancreatin (r) with CaCO<sub>3</sub> daily. August, 1910, discontinued all medication. Jan. 2, 1911, at work and quite well. Weight 158 pounds. Examination of one day's feces received on Jan. 27, 1911, rather large amount, color varying from brown to yellow, consistency, thick, pasty throughout, no lumps. Microscopic. A fairly large number of muscle fibers with striations intact. No nuclei seen. Numerous small and large fat globules (staining red with Sudan III). Urobilin abundant. Trypsin. Gross' test showed complete digestion of casein within fifteen hours.

April 26, 1911. Patient writes that he is doing an average amount of work and is in every way normal, except for some nervous excitability and an occasional slight attack of diarrhea. He weighs over 150 pounds, and has taken no medicine of any kind since last August, but still eats with regularity and care.

The cardinal symptoms of pancreatic insufficiency are diabetes, steatorrhea and azotorrhea. The last two alone are present in this case, indicating impairment of the external secretion only.

Chronic pancreatitis with indications so characteristic is relatively infrequent for several reasons (Oser<sup>1</sup>)

1 For each digestive function of the pancreas, ferments in one or more collateral organs exist (e g, lipase in the gastric juice, putrefactive enzymes in the intestine, proteolytic ferments in the gastric juice and succus entericus)

2 Santorini's duct may compensate entirely for the obliteration of the duct of Wirsung

3 A large part of the pancreas being functionally deficient, a small remnant will often suffice for the work required

4 Pancreatic disease is frequently combined with disease of neighboring organs

It has been suggested further, by A Schmidt and others, that in simple obstruction the ferments may reach the intestine by way of the circulation (Rosenberg explained the condition of his dog during the first month in this way See Table 2)

Before a diagnosis of chronic pancreatitis can be established, two other conditions must be considered in which azotorrhea and steatorrhea may occur i e, biliary obstruction and impaired intestinal absorption The first, although it had played an important part in this case, was excluded by the absence of jaundice at the time and for the previous nine months The character of the stools was distinctly pancreatic rather than biliary Such conditions as amyloid disease, atrophy of the intestinal mucosa, tabes mesenterica and tuberculous peritonitis were excluded by lack of confirmatory evidence, history of cholecystitis and most conclusively by improvement under organotherapy Accelerated peristalsis and intestinal catarrh can cause marked protein and fat losses

#### METABOLISM STUDIES

**Literature** Clinical and experimental cases of pancreatic insufficiency have been compiled in Tables 1 and 2, respectively They are selected chiefly with reference to studies in which the intake and output of protein and fat have been carefully compared The later ones, as in this case, illustrate the effect of various therapeutic measures, some older cases are included which exhibit features of special interest, although furnishing no quantitative data

Those of Kuntzman and Richard Bright were the first, in which the correlation of fatty stools with pancreatic disease was established Fles first noted the presence of unabsorbed protein in large amounts, as well as fat, and was able to vary these conditions at will by the feeding of fresh pancreas

The first quantitative studies were directed toward estimating the proportion of fat contained in the feces This has been done in many cases Muller gives 21 per cent as a normal figure Brugsch has con-

cluded that a fat content of over 30 per cent of the dry weight of the feces suggests impairment in absorption. This can attain to 80 per cent in icterus and the average for pancreatic disease is 60 per cent. It may be much lower when azotorrhea is marked. The point is one of comparatively slight value, as Muller states in his classical "Untersuchungen uber Icterus"

Here he insists that the percentage of fat cleavage is far more significant. In his three cases, the average proportion of total fat found in split form is 39 per cent, 84.3 per cent is the figure which he gives as normal. Katz holds that a cleavage of less than 70 per cent indicates pancreatic impairment. Fitz,<sup>23</sup> in a compilation of ten cases of undoubted pancreatitis in which the fat cleavage was noted, finds variations all the way from 8.4 to 82.5 per cent. He concludes, that in general the view of Muller is borne out, that fat-splitting is diminished. In nine cases of Alexander and Uy, the split fat varied from 9 to 86 per cent. Brugsch, on the contrary, believes that in acute and chronic pancreatic disease, the fat splitting is practically uninfluenced. The soaps may be diminished in amount on account of decreased alkalinity.

The absorption of nitrogen and fat in pancreatic insufficiency was first studied quantitatively in the well-known work of Abelman. This was done on Minkowski's dogs, immediately after the latter with von Mering had demonstrated the relation of pancreatectomy to diabetes.

Abelman obtained a higher degree of absorption when fat was fed in emulsified form (especially as in milk), nitrogen and fat absorption were both improved by the feeding of pigs' pancreas or "pancreatinum."

Brugsch found, in contradiction to Abelman, that fats in non-emulsified form are not wholly unabsorbable for totally pancreatectomized dogs. He further believes that, in the human intestine, milk is no better absorbed in pancreatic insufficiency than non-emulsified fats.

In thirteen of the clinical cases since that time, the average absorption of fat has been 45.2 per cent of the intake (where the effects of organotherapy are excluded). The figures, however, have varied widely. In one of Brugsch's cases with complete biliary and pancreatic obstruction, 11 per cent only was absorbed, while in the present case, on a low diet with fat given chiefly as milk, 95.7 per cent was absorbed without therapy. There is good evidence that fat absorption fares worse when pancreatic disease is complicated with icterus.

In regard to nitrogen absorption, we have a more constant finding in the various cases reported. It is rarely found below 50 per cent or above 80 per cent in chronic pancreatitis. The average of eleven cases in Table 1 (therapeutic effects excluded) is 63.2 per cent. Brugsch's 75 to 80 per cent probably places it too high. He regards the nitrogen disturbance as quite secondary in importance to that of fat. Weintraud, on the other hand, probably came nearer the truth in attributing to the

TABLE 1—CLINICAL PANCREATIC DISEASE

Author	Date	Diagnosis	Glycosuria	Jaundice	Per Cent N. Ab-sorption	Per Cent Fat Ab-sorption	
Kuntzmann <sup>2</sup>	1820	Induration of pancreas, duct obliterated	0	+		Low	First correlation of fatty stools with pancreas
Blight <sup>3</sup>	1833	Carcinoma of pancreas	+	+		Low	Seven pancreatic cases in all, one other had fatty stools
Fies <sup>2</sup>	1864	Carcinoma of pancreas	0	0		Low	
Ziehl <sup>2</sup>	1864	Chronic pancreatitis	+		Low	Low	First noted azotorrhoea, condition of stools varied at will by feeding calves' pancreas
	1883	Carcinoma of pancreas, duct closed	0	0		Low	50 per cent of dried stool-fat
Demme <sup>2</sup>	1884	Congenital syphilis pancreas and liver	0	+		Low	64.73 per cent fat
		Obstructed duct	0	+	Low	Low	
Muller <sup>4</sup>	1887	Cyst of pancreas	0	0	Low	Low	30 per cent of fat split in average of three cases, 84.3 per cent given as normal amount split
		Pancreatic calculus with atrophy	+	0	Low	Low	
Le Nobel <sup>5</sup>	1888	Chronic pancreatitis	+	0		Low	No fatty acid or indican, thought maltosuria important
		Necrosis of pancreas				Low	29.5 per cent of fat split
Von Noorden <sup>6</sup>	1890	Carcinoma of pancreas				Low	8.4 per cent of fat split
							Feces obtained at autopsy
Hirschfeld <sup>7</sup>	1891	Probable pancreatitis (6 cases)	+	0	68.2	65.2	Icterus in one case
Oser <sup>1</sup>	1893	Chronic pancreatitis	0	+		Low	46 per cent of dried stool-fat
Weintraud <sup>2</sup>	1898	Chronic pancreatitis			54—58	78—75	Says N disturbance more important than fat in pancreatic disease
		Carcinoma pancreas	+	0	70.4	17.1	
Deuchers <sup>8</sup>	1898	Carcinoma pancreas	0	+	81.0	47.4	Average iccithin output 0.3 gm in three cases
Katz <sup>3</sup>	1899	Indurated pancreas with hemorrhage and necroses		+		Low	80 per cent of fat split
							62 per cent of fat split
Northrup and Heiter <sup>9</sup>	1899	Carcinoma pancreas	0	+		Low	13.93 per cent of fat split
							82.5 per cent of fat split

[illegible]

TABLE 2—EXPERIMENTAL PANCREATITIS IN DOGS

Author	Date	Condition	Per Cent N Ab- sorption	Per Cent Fat Ab- sorption	
Abelmann <sup>18</sup>	1890	Total extirpation of pancreas (18 cases)	Average 44	00	Non emulsified fat fed
				18.5	Emulsified fat fed
				50-53	Milk fed
				48-72	Pigs' pancreas fed
					"Pancreatinum" fed
Cavazzani <sup>12</sup>	1893	Partial extirpation of pancreas (12 cases)	Average 54	25-65	Emulsified fat fed
				65-80	Milk fed
				Low	Animal scorned fat, took soaps greedily
Baldi <sup>12</sup>	1894	Total extirpation of pancreas		Low	Large amounts of oily fat in stools
Sandmeyer <sup>19</sup>	1895	Nearly total extirpation of pancreas (several cases)	62-70	0-78	Raw pancreas raised absorption, non emulsified fat fed
				42	Emulsified fat fed
Rosenberg <sup>20</sup>	1896	Animal living 11 months with ligated pancreatic duct	Low	Low	No change first month
Oser and Katz <sup>1</sup>	1898	Ligation of pancreatic duct	Normal	Normal	48 per cent of fat split
		Total extirpation of pancreas	Low		Several cases
Zunz and Mayet <sup>21</sup>	1904	Ligation of pancreatic duct in 50 dogs	Normal	Normal	Severe diabetes forty one days
		"Subtotal" pancreas extirpa- tion		Low	
Brugsch	1906	Total pancreas extirpation		81	Milk diet
				95	Olive oil diet
				50	Milk diet
				9-20	Meat diet
Camus and Nicloux <sup>22</sup>	1910	Ligation of biliary and pan- creatic ducts		33-37	Without "Iipascidine"
				63.8	With "Iipascidine"



nitrogen absorption figure, the greater importance in pancreatitis. It is more consistently low, and its significance is neither so much obscured by a complicating biliary obstruction nor as markedly affected by variations in diet as is the fat. A third factor which may complicate the fat metabolism, is the diabetic acidosis. Brugsch brings this forward to explain Sandmeyer's experimental work (Table 2), in which the latter obtained absorption figures for fat varying from 0 to 78 per cent.

Our metabolism work (Table 3 and Chart 1) is divided into three periods: Nov. 23-29 (no therapy), Nov. 30-Dec. 4 (hydrochloric acid dil.  $\text{M}_{\text{N}}$  with meals), Dec. 5-6 (pancreatin gr. vi, t. i. d.). The Schmidt-Strasburger<sup>24</sup> diet was given for the first four days. It contains in one day's portion 1.5 liters milk, 100 gm zwieback, 2 eggs, 50 gm butter, 125 gm beef, 190 gm potatoes, 80 gm oatmeal. This represents about 10.9 gm nitrogen, 111 gm fat and 191 gm carbohydrate, and is given in five separate meals. A mixed diet was given on the two following days, no analyses being made, after which were given special diets No. 3 and No. 4. These were similar to the Schmidt-Strasburger diet and the amounts of nitrogen and fat contained in each are noted in Table 3.

The total urine and feces for each 24-hour period was collected daily at 7 a. m. The analyses of excreta received on any given day are tabulated under the date immediately preceding.

The nitrogen estimations were made by the Kjeldahl method, and the fat was obtained by the usual ether Soxhlet extraction. In general the laboratory procedures were the same as those employed by Brugsch.

The tables show that the nitrogen absorption during the first period averaged 55.8 per cent of the amount ingested. Hydrochloric acid was given during the second period, at the suggestion of Professor Barker, in the hope of favoring pancreatic activity by the stimulation of secretin, the patient's condition being one of marked anacidity as stated above. The nitrogen absorption, however, fell to an average of 47.6 per cent for these five days, thus confirming the statement of Ehrmann and Lederer<sup>25</sup> that achylia and anacidity are favorable rather than inimical to pancreatic function. During the "pancreatin" period, the nitrogen absorption corresponded very closely to that of the first period.

In none of the four fat analyses were abnormal figures obtained, and we have noted above that the striking butter-like stools of the first few days were soon replaced by stools of a liquid brown character. The only explanation of this lies in the fact that after admission to the hospital, the diet contained limited amounts of fat given in easily absorbable form.

The nitrogen balance remained normal throughout the experimental period indicating that, in spite of deficient absorption, the patient was not forced to draw on his rather meager supply of tissue protein during this time.

The administration of pancreatin-rhenania with alkali followed a few days after the conclusion of the metabolism studies, and rapid improvement then ensued.

TABLE 3

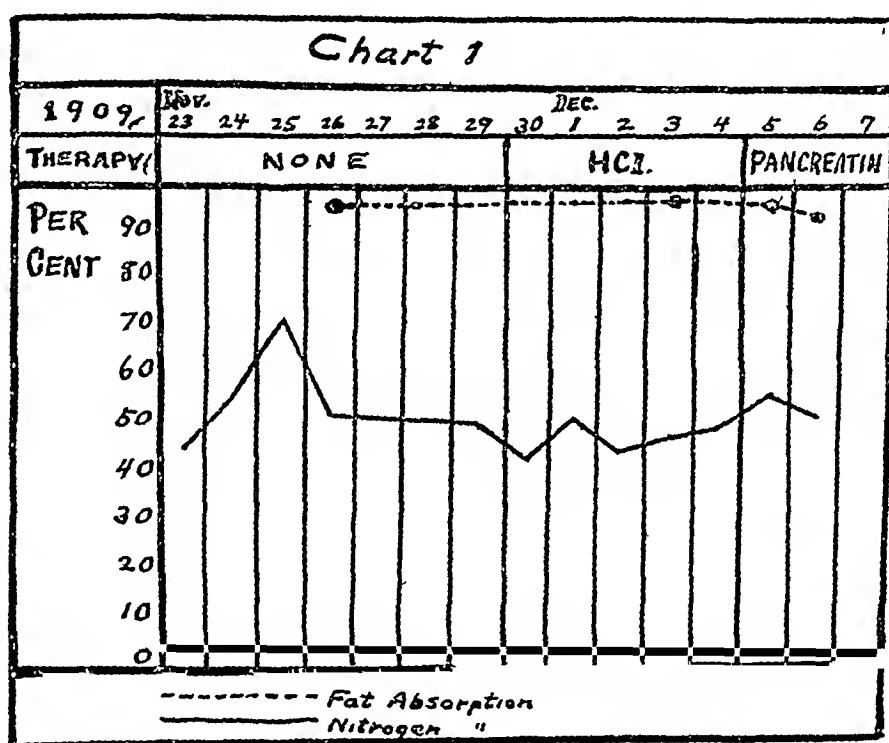
		November										December						
		23	24	25	26	27	28	29	30	1	2	3	4	5	6	7		
Diet		Schmidt-Straßburger N = 10.9 Fat = 111.0					Mixed	No 3 N = 5.98 Fat = 61.76					No 4 N = 4.96 Fat = 70.05					
Therapy		None										Hydrochloric Acid					Pancreatin	
Urine	Total amount	620	1,050	790	1,450	1,190	740	935	410	1,040	920	860	600	550	300	440		
	Nitrogen	6.3	6.4	6.9	5.2			2.76	2.60	1.98	2.87	2.00	2.96	3.00	2.01			
Feces	Dry weight	13.06	29.36	12.64	12.10	21.22	13.88	4.12	6.99	4.88	3.22	3.92	17.83	7.19	8.45			
	Nitrogen	5.9	4.9	3.0	5.1			3.00	3.35	3.00		3.02	3.46	3.06	3.32			
Per cent absorption	Nitrogen	45.9	56.0	72.5	53.3			51.1	44.0	51.1	45.2	47.9	50.0	56.1	52.3			
	Fat				95.7							97.8		96.4	94.1			
Nitrogen balance		-1.3	-0.4	+1.0	+6.0			-0.2	±0	+1.0	-0.1	-1.0	+0.4	+0.9	+1.6			

The relation of the nitrogen and fat to the total dry weight of the feces was nitrogen (average of thirteen analyses) 34.4 per cent, fat (average of four analyses) 40.5 per cent

#### OTHER FUNCTIONAL TESTS OF THE PANCREAS

Of the many tests devised for ascertaining the functional condition of the pancreas, but few have been proved of clinical value

As indicative of impairment of the internal secretion, Loewi<sup>26</sup> supplements the tests for glycosuria or low sugar tolerance, with his epinephrin mydriatic reaction. It is based on certain very obscure and complex relations between the glands of internal secretion and the nervous system,



on which the metabolism studies of Eppinger<sup>27</sup> and others bear very interestingly. The practical value of the reaction is far from being established.

For the study of the function of the external secretion are available, on the one hand, the end products of metabolism, and on the other, the amounts and distribution of the enzymes themselves.

In addition to determining the presence of azotorrhea and steatorrhea and the quantitative study of these conditions with relation to the diet, we applied Schmidt's nuclei test. Centimeter cubes of beet were enclosed in silk and hardened in alcohol. After washing with water for three hours, several of these were given to the patient. They were later recovered in the stools and studied microscopically after treating with acetic acid. Very few nuclei were found intact. This negative result is

of little value as regards the action of the pancreatic juice, for nucleases, irrespective of trypsin, may occur in the intestinal tract. Had large numbers of nuclei been found, however, or had only the peripheral fibers of each cube given evidence of digestion, the result would have been very suggestive of pancreatic insufficiency.

The amount of lecithin in the feces was comparatively large in Deucher's three cases of pancreatitis, and later workers have not disproved that such an increase may be of value as a functional indicator.

Gerhardt,<sup>28</sup> in 1886, stated that, especially in intestinal obstruction, a low output of indican signifies decreased proteolysis, due to pancreatic insufficiency. Later observations on this point have been widely diverse, an increased output being shown in many cases. Controlled tests showed no indicanuria in the present case, but it must be borne in mind that peristalsis was rather rapid.

The pancreatic ferments themselves are made the basis of certain functional tests. For trypsin in the feces, we employed the casein test of Gross.<sup>29</sup> It is based on the fact that casein in an alkaline solution will disappear in the presence of trypsin. The addition of dilute acetic acid demonstrates the presence or absence of casein after time has been allowed for digestion. Trypsin was present in the feces during our metabolism work and in January, 1911.

Goldschmidt<sup>30</sup> offers a quantitative modification of the Gross test.

Schlecht,<sup>31</sup> following E. Muller, demonstrates proteolytic action by the formation of a hole in solidified serum, on which a drop of the ferment-containing fluid has been placed.

Sahli's<sup>32</sup> well-known glutoid capsules resist gastric action, but are soluble in pancreatic juice. An indicator, such as iodoform, is thus set free in the duodenum, and may be detected in the saliva or urine. This, again, has been found an unsatisfactory test for pancreatic impairment. Its chief value is in indicating the motility of the stomach.

The feces may be tested for lipase with the ethyl butyrate test of Kastle and Loevenhart.

The third pancreatic ferment, diastase, was neglected as an indicator until 1907, when Ambard, Binet and Stodel<sup>33</sup> suggested that tests be made for it after administration of a purgative. Purgings in the normal individual produces a stool containing abundant diastase. This test has been extended by Wynhausen,<sup>34</sup> using the method of Wohlgemuth, for detection of the ferment.

We are not confined to the feces, however, for evidences of pancreatic juice in the alimentary canal. Boldyreff<sup>35</sup> has shown that an "oil breakfast" will cause a back flow of pancreatic juice and bile from the duodenum into the stomach. He gave 100 to 200 c.c. of 2 per cent oleic acid in olive oil. One-half to an hour later he removed the stomach

contents, in which could be demonstrated the pancreatic ferments Volhard states that olive oil alone may be used According to Ehrmann and Lederer, the stomach contents, if acid, should first be neutralized

Salomon suggested the feeding of "pancreon" and similar preparations as a therapeutic test of pancreatic insufficiency

The much discussed reaction of Cammidge<sup>38</sup> has yet to be mentioned This worker has claimed a specificity for certain crystals obtained after a complicated chemical procedure in the urine of pancreatitis Much evidence has now accumulated to indicate that the test is not only cumbersome, but almost without significance Last year Dr G H Whipple<sup>37</sup> and others showed that similar crystals may be obtained from the products of autolysis of tissues and other sources Negative tests were obtained in fifteen of nineteen cases of pancreatitis reported by Deaver<sup>38</sup> in his recent discussion of chronic pancreatitis from a surgical standpoint Kinney has reported 154 various cases in which the test has been applied

Cammidge himself has modified his procedure in several ways For example, 10 c c of urine was at first asserted to suffice for the reaction, while his present method requires 4 liters — a very suggestive discrepancy.

Using the "C" reaction, 50 c c of urine from this patient gave a negative result When 4 liters were taken, large yellow "sheaves" were isolated which dissolved in dilute sulphuric acid Their melting point, however, was 130 F, instead of 170 to 180 F, as observed by Cammidge

#### CONCLUSIONS

1 The case described is one of chronic insufficiency of the external secretion of the pancreas subsequent to acute cholecystitis

2 There has been no diabetes at any time

3 While azotorrhea and steatorrhea were both marked features on admission, the fat absorption was over 95 per cent during the metabolism observations

4 The nitrogen absorption during a period without therapy averaged 55.8 per cent While hydrochloric acid was given, the average was 47.6 per cent During the feeding of pancreatin (not rhenania) 54.2 per cent of the ingested nitrogen was absorbed

5 The nitrogen balance was normal during the metabolism work

6 Rapid improvement followed the administration of pancreatin (rhenania) and calcium carbonate

7 None of the other functional tests applied to the case gave significant results

8 From 4 liters of urine atypical "Cammidge crystals" were isolated

It affords me the greatest pleasure to express to Professor Barker my gratitude, not only for the opportunity of carrying on this work in the wards and the chemical laboratory of the medical clinic, but also for his kindly interest in the work and his many helpful suggestions

I am further very much indebted to Dr E A Slagle for most valuable assistance in the chemical work

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# THE METABOLISM IN A CASE OF IDIOPATHIC OSTEOPSATHYROSIS \*

A BOOKMAN, M D

NEW YORK

To the kindness of Dr B Sachs, to whose service at Mt Sinai Hospital this case was admitted on Oct 16, 1909, is due the opportunity of making this study. A synopsis only of the history and clinical features is given, as the case will subsequently be presented from the clinical point of view by another hand.

*Patient*—B G, male (admission number 111186), family history and previous history yield nothing of importance. Venereal infection denied, no drug habits, no acute infection preceding onset.

*Present Illness*—About fourteen months before admission patient broke right humerus in the upper third with very slight trauma. Two weeks after this injury he broke the left humerus in the upper third while raising the window. Both fractures healed very quickly. Following these injuries patient noticed that he was growing weak and thin, the muscles of both arms were beginning to atrophy and his strength rapidly diminished. Before the illness patient weighed 130 pounds. The atrophy of the arm muscles was followed by a rapid wasting of all the skeletal muscles. For twenty-four weeks previous to admission he has been unable to walk, and raises himself to a sitting posture with great difficulty, no pain or paresthesias. Five weeks before admission a bottle fell on his right arm and cracked the bone, as shown by x-ray. This fracture has since healed. Of late he has been complaining of headaches, no vertigo, no difficulty in swallowing, no urinary disturbance, bowels constipated, appetite fair, vision and hearing good.

*First Physical Examination*—October 16, 1909. General condition poor, patient pale and emaciated.

*Head* Fairly well formed, forehead receding. Expression dull, no skull tenderness, marked general alopecia. Speech normal.

*Eyes* Right pupil somewhat larger than left and irregular, pupils react promptly to light and accommodation. No palsies of orbital muscles, no nystagmus. Conjunctivæ pale, corneal reflex present.

*Face* No palsies, jaw reflex present, sensations normal.

*Mouth* Teeth and gums in very poor condition, marked fetor. Throat negative. Pharyngeal reflex present.

*Skin* Few scattered scars on back and extremities, not pigmented.

*Glands* Palpable inguinals, axillaries, posterior cervical and small epitrochlears.

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\*From the Laboratory of Physiological Chemistry, Mount Sinai Hospital, New York.

Thyroid Showed no evidence of abnormality

Chest Marked atrophy of all muscles Narrow, emphysematous, marked depressions above and below clavicles

Lungs Posteriorly, marked hyperresonance over bases, otherwise negative

Heart Showed no abnormality Marked sclerosis of radial arteries Tension normal

Liver and Spleen Negative

Abdomen Superficial reflexes present, cremasteric reflexes present No abnormality

Genitals Negative

Extremities Upper, No ataxia, no tremor In upper part of left humerus there was a callus at site of the old fracture At junction of upper third and lower two thirds of right humerus there was slight thickening of bone (old fracture)

Lower Patient walked with great difficulty, gait uncertain, waddling, "goose-like" Power in both legs equally diminished in all groups of muscles No ataxia or tremor Knee-jerks increased on both sides, achilles reflexes increased No clonus, Babinski, Mendel, nor Oppenheim Sensation normal

October 18 (Dr Sachs) Atrophy (especially of arm and leg muscles), and stiffening Considerable stiffening of upper part of spinal column Forearm muscles little affected, deltoids hardly Interosseous spaces in both hands very distinct Hand muscles wasted, especially hypothenar of left hand Reflexes of upper extremities lively On striking forearm at any point there is contraction of biceps and pectoral group of same side Grasp of both hands good Difficulty in getting up from chair Patient rises from chair as one suffering from muscular dystrophy and shows weakness of the deep spinal muscles below the mid dorsal level When placed on the floor and asked to rise, he is unable to do so, chiefly on account of the weakness of the spinal muscles Marked atrophy both anteriorly and posteriorly of leg and arm muscles There is no bulbar paralysis present All muscular groups of extremities respond to strong faradism only In some groups the response is feeble No fibrillary twitchings

*Course of Disease*—October 30 Sputum negative for tubercle bacilli

November 2 Condition much better, gained nine pounds since admission and is much stronger Able to rise from floor, but still with great difficulty Local muscular irritability less marked Otherwise no change

November 3 No disturbance of pain or temperature sense

Discharged Nov 15, 1909

Readmitted Dec 13, 1909

Jan 1, 1910 Complains of some pain in legs, has gained considerably in weight Able to rise from floor with assistance Gait still waddling Weakness of ilio psoas muscles chiefly, gluteal wasting Wasting of arm muscles, less of intrinsic hand muscles Reflexes unchanged

January 10 On discharge, condition about same as on admission, slight gain in weight

Readmitted Dec 20, 1910, complaining of marked weakness

*Second Physical Examination*—General condition fair, marked emaciation Pupils equal, reacting Upper extremities Limitation of motion of right shoulder joint and slight of left shoulder Marked atrophy of muscles of both forearms Lower extremities Loss of power in right leg, power slight in left Marked atrophy in muscles of thigh In middle of right tibia, on anterior sur-



face, was a small swelling about three-fourths of an inch in diameter, fluctuating, not tender, slightly movable Otherwise unchanged since last stay in hospital Vomited frequently on and after December 23

Died Dec 29, 1910 An autopsy was not permitted

Temperature during patient's earlier stays in hospital always below 99 A few days before death reached 99.4 F, and pulse which had previously been normal in frequency, ranged between 90 and 110 Respirations, except during terminal period, normal in frequency

Wassermann and Noguchi reactions, Nov 12, 1909 Negative (Dr D J Kaliski)

*Blood Examination*—Oct 19, 1909 W B C 11,000, R B C 4,300,000, hemoglobin 85 per cent Differential count Polynuclears 76 per cent, large lymphocytes 14 per cent, small lymphocytes 10 per cent

November 2 Blood-pressure Right arm, 143 mm mercury Left arm, 138 mm mercury

#### Weights

Oct 17, 1909	86	pounds
Oct 22, 1909	89	pounds
Oct 24, 1909	92½	pounds
Oct 31, 1909	95	pounds
Nov 7, 1909	94	pounds
Nov 14, 1909	96	pounds
Dec 17, 1909	95	pounds
Dec 24, 1909	94½	pounds
Dec 26, 1909	95	pounds
Jan 3, 1910	98	pounds
Jan 10, 1910	97	pounds

Weight not recorded during last stay in hospital

Average daily amount of urine passed during stay in hospital 2200 cc Specific gravity of single specimens varied from 1004 to 1034, faint traces of albumin, no sugar, acetone, nor diacetic acid was found at any time Hyaline and granular casts in small number were repeatedly found

*Röntgen Ray Examination* (Dr L Jaches)—Oct 24, 1909 One radiographic plate of the left shoulder shows the head, anatomical and surgical necks of the humerus to be cystic, the shaft shows a sponge-like appearance

Oct 27 Two radiographic plates of hips and right shoulder-joint show cystic condition of bones with partial and irregular absorption

If this case be considered one of osteopsathyrosis, it is in some respects unique, viz

- 1 It showed marked and general muscular atrophy and weakness
- 2 It was accompanied by polyuria
- 3 It came at a more advanced age than most of the cases on record
- 4 There is no hereditary element in the etiology

As far as could be ascertained, there is in the literature of this disease only one case<sup>1</sup> in which special mention is made of the presence of

<sup>1</sup> Schultze, I Arch f klin Chir (Langenbeck's), 1894, LVII, 329

muscular atrophy Here it is mentioned that with otherwise well-developed musculature, there was marked atrophy of the muscles of the calves The presumption is that it was due to disuse Poirrier<sup>2</sup> regards the muscular atrophy as the result of multiple fractures This atrophy he states, most often relates only to the muscular groups in relation to the fractured bone Larat, Roger and Voisin,<sup>3</sup> in a recent study of the muscular reactions in their case found marked diminution of the electrical reaction of the muscles, this being general and not confined to the site of fracture They consider the muscular lesions as contemporaneous with the osseous changes, as they appear to have been in the present case

As to the chemical composition of the bones in osteopsathyosis, we have only the statement of Endeilen, who reports that in his case there was an increase of organic substance and a decrease of mineral matter The diagnosis in this case, however, appears to be open to doubt<sup>4</sup>

No case of osteopsathyosis has been investigated with reference to the metabolism The only statement bearing on it is that of Blanchard, who found an increase of  $P_2O_5$  in the urine This finding taken by itself is of no value

#### RESULTS OF METABOLISM DETERMINATION

##### I DAILY URINARY RESULTS

Date	Total N	Creatinin	Creatinin N	Creatinin N in % of Total Urinary N	Amount in cc
12/19/09	11 656	0 9525	0 353	3 02	2350
12/20/09	13 294	0 764	0 283	2 12	2380
12/21/09	9 243	0 634	0 235	2 55	1680
12/22/09	13 995	0 942	0 349	2 49	2840
12/23/09	10 643	0 709	0 263	2 47	2210
12/24/09	8 561	0 554	0 205	2 39	2080
Totals	67 392	4 528	1 688		

Creatinin coefficient =  $\frac{\text{mgm creatinin nitrogen excreted daily per kilo body weight}}{0.281} = 0.0065$   
43

Average of daily creatinin nitrogen in percentage of total urinary nitrogen = 2.5

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## II SUMMARY OF RESULTS FOR SIX-DAY PERIOD

Element	Urine	Feces	Total Excreted	Total in Food	Balance
CaO	6 2826	7 2853	13 5679	8 6279	— 4 94
MgO	0 5711	0 7576	1 3287	1 1458	— 0 1829
Total P	2 5666	0 8601	3 4267	3 986	+ 0 5593
Total S	6 3838	0 7822	7 166	8 0642	+ 0 8982
Total N	67 392	10 904	78 296	89 085	+10 789

## III ANALYTICAL METHODS

The metabolism was studied for a period of six days, the patient being allowed to eat freely of the ordinary hospital diet. Each portion was weighed or measured and an equal amount was sent to the laboratory for analysis. All the food was collected for the period, dried on the water-bath, reduced to a fine powder and sampled for analysis.<sup>5</sup> Only distilled water was consumed. Salt, butter and bread were weighed off in a quantity sufficient for the six days. The amount used was computed and these substances, except the butter, were added in appropriate amounts to the samples of food taken for analysis. Butter. For calcium, magnesium and total phosphorus 30 gm were digested in Kjeldahl flask with  $\text{H}_2\text{SO}_4$ , made up to 1000 cc and of this solution 100 cc taken for each analysis. Total sulphur was not determined in butter on account of the difficulty encountered in making fusions. Neuberg<sup>6</sup> states that there are only traces present.

The stools were marked off with charcoal at the beginning and the end of the period.

Urine was collected for each twenty-four hour period, and separate determinations of nitrogen, creatin and creatinin were made.

Total sulphur, total phosphorus, calcium, and magnesium were determined on a mixed specimen consisting of aliquot parts of each day's urine.

All determinations were made in duplicate, and analyses were repeated when the results for the pairs did not agree.

Total nitrogen—Kjeldahl

Creatin and creatinin—Folin

Magnesium and calcium—According to the method of McCrudden<sup>7</sup> except that the calcium was weighed as  $\text{CaSO}_4$ .

Total phosphorus and total sulphur—Fusion with solid sodium hydrate and potassium nitrate. Fusion mass dissolved in hot water, made strongly acid with  $\text{HNO}_3$  and precipitated as ammonium phosphomolybdate, which was dissolved in ammonia, precipitated as  $\text{Mg NH}_4\text{PO}_4$  and weighed as  $\text{Mg}_2\text{P}_2\text{O}_7$ . Total sulphur weighed as  $\text{BaSO}_4$ .

The diet for six days was as follows

Dec 18 Milk, 32 oz, Meat, 147 gm, Vegetable, 210 gm, Soup, 14 oz, Crackers, 17 gm, Zwieback, 10 gm, Oatmeal, 120 gm, Egg, 47 gm, Water, 24 oz

<sup>5</sup> McCrudden, F. H. Jour Med Research, 1903, iv, 135

<sup>6</sup> Albu and Neuberg. Physiologie und Pathologie des Mineralstoffwechsels, Berlin, 1906

<sup>7</sup> McCrudden, F. H. Jour Biol Chem, 1910, vii, 83

- Dec. 19 Oatmeal, 120 gm , Milk, 24 oz , Egg, 180 gm , Cracker, 17 gm , Water, 40 oz , Zwieback, 17 gm , Meat, 195 gm , Cocoa, 8 oz , Potatoes, 120 gm , Custard, 30 gm , Ice Cream, 65 gm , Apple Sauce, 140 gm , Prunes, 55 gm
- Dec 20 Meat, 92 gm , Oatmeal, 117 gm , Cabbage, 112 gm , Milk, 16 oz , Custard, 40 gm , Water, 40 oz , Soup, 8 oz , Cocoa, 8 oz , Cream, 1 oz , Potatoes, 110 gm , Orange Juice, 3½ oz , Rice, 145 gm , Farina, 183 gm , Egg, 93 gm
- Dec 21 Oatmeal, 45 gm , Water, 48 oz , Milk, 40 oz , Cocoa, 8 oz , Meat, 75 gm , Rice, 135 gm , Potatoes, 114 gm , Custard, 75 gm , Prunes, 60 gm , Soup, 8 oz , Cream, 1 oz , Apple Sauce, 175 gm , Egg, 94 gm
- Dec 22 Oatmeal, 220 gm , Egg, 160 gm , Milk, 40 oz , Water, 40 oz , Chicken, 60 gm , Rice, 180 gm , Potatoes, 150 gm , Soup, 8 oz , Custard, 35 gm , Cream, 1 oz , Farina, 205 gm
- Dec 23 Oatmeal, 200 gm , Egg, 45 gm , Milk, 16 oz , Water, 32 oz , Cocoa, 8 oz , Potatoes, 100 gm , Soup, 8 oz , Chicken, 70 gm , Rice, 160 gm , Cabbage, 100 gm
- From Dec 18 to 23 Bread, 639.2 gm , Butter, 92 gm , Salt, 13 gm

Except in one particular — the small retention of magnesium — my results are strikingly similar to those of McCrudden<sup>8</sup> and the less complete findings of earlier workers on the metabolism in osteomalacia. It will be noted that hand in hand with a retention of nitrogen went a relatively enormous loss in calcium and a retention of sulphur and of phosphorus. The loss of calcium occurred in spite of a large excess of this element in the food over the normal needs of the human body. Towle<sup>9</sup> found that CaO, 0.014 gm per kilo body weight, were needed daily. Renvall<sup>10</sup> found that an adult man needed Ca 0.7 (CaO 0.98) per day. The patient under consideration received daily CaO 1.322 = 0.03 per kilo.

In this case the muscular atrophy and weakness were prominent factors, and it is of interest to note that in part the findings are paralleled by those in cases where muscular atrophy was not complicated by such obvious bone lesions.

Thus, Johannes Mueller<sup>11</sup> states that in a case of progressive muscular atrophy, there was found an increased excretion of sulphur and calcium. This, however, he ascribes to a secondary atrophy of the bones. Pemberton, in a case of myasthenia gravis, found a marked loss of calcium amounting to 8.888 gm in the ten days of the investigation. In another paper<sup>12</sup> he states that no study of calcium metabolism is on record, in either muscular dystrophy or Thomsen's disease. In his case

8 McCrudden, F. H. *Am Jour Physiol*, 1905, xiv, 211, 1906, xvii, 211

9 Towle *Am Jour Med Sc*, 1910, cxl, 100

10 Renvall, G. *Skand Arch f Physiol*, 1904, xvi, 94

11 Mueller, Johannes. *Habilitationsschi*, Wurzburg (Abstr. in *Arch f Verdauungskrankh*, 1897-98, iii, 282)

12 Pemberton *Am Jour. Med Sc*, 1911, cxli, 253

of myotonia atrophica, studied for five days, with a positive nitrogen balance of 28 265 gm there was a negative calcium balance of 0 566 gm

In both of the above muscular diseases he found a decrease of creatinin in the urine as compared with the normal Spriggs<sup>13</sup> found a similar relationship in progressive muscular dystrophy, myasthenia gravis and amyotonia congenita

The creatinin findings in the case under consideration were not obtained on a meat-free diet On this account the creatin values are not given The amount of preformed creatinin is, however, so little affected by a moderate amount of meat in the diet<sup>14</sup> that we can disregard this factor The creatinin ratio in this case was only slightly below the normal, which is from 7 to 11 mg, although the percentage of creatinin-N to total urinary N is considerably below that found in normal cases (3 9) Whether this relationship alone would justify a conclusion that the muscular changes present played a minor rôle in the causation of changes in the mineral metabolism can be determined only by further calcium and creatinin determinations in suitable cases

Mention has already been made of the similarity of the findings in this case to those in osteomalacia The latter disease has been checked by castration, and McCrudden, in his case, found the consequent improvement in the symptoms to be accompanied by calcium retention, where before there had been a loss Similar results were obtained by Neumann Of late this disease has been shown to be amenable in some cases to injection of epinephrin<sup>15</sup> Bossi<sup>16</sup> also believes that this substance has a similar influence in the pelvic deformities of rickets

Carnot and Slavu<sup>17</sup> have shown that in dogs injected subcutaneously with epinephrin (*chlorhydrate d'adrénaline*) ossification is much greater than in controls They state that it seems to cause calcium retention

These facts and many others point to a close relationship between changes in the bones and in calcium metabolism, and the functions of the organs of internal secretion Thus, Tansk and Vas<sup>18</sup> found a slight loss of calcium in acromegaly Oberndorffer<sup>19</sup> found a much more marked

13 Spriggs Quart Jour Med, 1907, 1, 68

14 Van Hoogenhuysse and Verploegh Ztschr f physiol Chem, 1908, lvi, 161  
Folin, O Festschr f Hammarsten, Upsala, 1906, Klercker, Otto af Beitr z chem Physiol u Pathol, 1906, viii, 60 Shaffer, P A Am Jour Physiol, 1908, xxi, 449

15 Bossi Centralbl f Gynak, 1907, Nos 3 and 6 Stocker Corr-BI f Schweiz Aerzte, 1909, xxxix, 433

16 Centralbl f Gynak, 1907, xxxi, 1560

17 Carnot and Slavu Soc biol, 1910, lvi, 832

18 Tansk and Vas Pest med-chir Presse, 1899, xxxv, 194

19 Oberndorffer, E Ztschr f klin Med, 1908, lxy, 6

loss amounting to CaO 8.77 gm in a ten day period. In cretinism ossification is delayed.<sup>20</sup>

Various observers have recently shown in experiments in animals that thymectomy leads to marked changes in the bones, rendering them softer and more flexible,<sup>21</sup> or leading to spontaneous fracture.<sup>22</sup> These changes are especially marked in very young animals in which the bone is found to be largely replaced by cartilage.<sup>23</sup> Klose and Vogt<sup>24</sup> have found that this operation causes a reduction of more than one-half in the calcium content of the bones, and Fraenkel<sup>25</sup> states that the thymectomized animals excrete more than twice as much calcium as the controls.

Parathyroidectomy, McCallum<sup>26</sup> found, caused in dogs an increase in calcium in the urine. Other observers have had varying results.

For the hypophysis Franchini<sup>27</sup> has found that injection of its extract causes a marked calcium and magnesium deficit, and a smaller loss in phosphorus. The influence of the isolated posterior lobe on metabolism was especially profound. Falta<sup>28</sup> also states that the hypophysis has a very marked influence on calcium and magnesium metabolism. Malcolm<sup>29</sup> found that feeding the dried glandular portion caused increased calcium excretion with a considerable increase also in magnesium, and that the dried nervous portion also increases calcium excretion, but that magnesium is less affected. With the fresh gland, however, calcium retention ensued.

These facts have been mentioned because the coincidence of rapid wasting, spontaneous fractures, and a marked polyuria (which does not seem to be adequately explained by the slight evidences of nephritis) seems to point to some disturbance of the organs of internal secretion. That the hypophysis may have played an important part here is suggested by Cushing's summary<sup>30</sup> of the results of injection and feeding experiments with this gland. He states that "in the posterior lobe or its epithelial investment is a substance which raises blood-pressure, dilates the pupil, causes diuresis, and, when given subcutaneously or injected over long periods of time, is likely to produce marked nutritional disturbances."

20 Schmidt, M. B. *Ergebn d. allg. Path.*, 1897, iv, 617.

21 Basch. *Jahrb. f. Kinderh.*, 1906, lxxiv, 285.

22 Klose. *Arch. f. Kinderh.*, 1911, lv, 1.

23 Soli. *Arch. ital. de biol.*, 1909, lvi, 217.

24 Klose and Vogt. *Beitr. z. klin. Chir.*, 1910, lxxv, 1.

25 Fraenkel, S. *Dynam. Biochemie*, Wiesbaden, 1911, 447.

26 McCallum and Voegtlin. *Bull. Johns Hopkins Hosp.*, 1908, xlv, 91.

27 Franchini. *Berl. klin. Wchnschr.*, 1910, xlvii, 613.

28 Falta. *Wien. klin. Wchnschr.*, 1909, lxx, 1059. Falta and Ivovic, *ibid.*, p. 1806.

29 Malcolm, J. *Jour. Physiol.*, 1903, xxv, 270.

30 Cushing, H. *Amer. Jour. Med. Sc.*, 1910, cxxxix, 475.

While the facts in this case point toward a disturbance of the organs of internal secretion, it is not intended to select one or another of them as the one primarily at fault. Both experimental and clinical investigations show that a disturbance of one of these glands is quickly followed by changes in others of the system.

McCrudden<sup>31</sup> has already suggested an etiological similarity between rickets, osteitis deformans, and senile and puerperal osteomalacia, and to this we may add osteopsathyrosis. If the common factor in these conditions should prove to be some disturbance of the organs of internal secretion, this case would add evidence that they also play an important part in the pathology of the muscular atrophies.

I wish to express my thanks to Dr. I. Abrahamson for many kindnesses in connection with the work, and to Dr. S. Bookman for suggestions in regard to the analyses.

40 East Sixty-Second Street

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31 McCrudden. *THE ARCHIVES INT. MED.*, June 15, 1910, v, 630.

# THE COAGULATION-TIME OF THE BLOOD AS AFFECTED BY VARIOUS CONDITIONS

MYER SOLIS COHEN, M D

PHILADELPHIA

An estimation of the coagulation-time of the blood is of little value unless one is acquainted with the many factors that affect it. Some of these factors are extrinsic, acting on the shed blood, others are intrinsic, acting on the blood while it is still in the vessels. Of the former factors many are introduced by the method employed for measuring the clotting-time. The clotting-time obtained by any one of the different methods employed is influenced by the factors of error inherent to that method. It is important, therefore, to be familiar with the sources of error inherent in the method used.

## 1 METHODS EMPLOYED FOR MEASURING THE CLOTTING-TIME OF THE BLOOD

The methods employed for measuring the coagulation-time of the blood may be grouped according to the similarity of the factors involved. In one group the blood is received in capillary tubes, in another on wire loops, the contour of the drop is observed in several methods, the movement of the corpuscles when a current of air is directed against the drop in others, and the first appearance of shreds of fibrin in the drop in still others. Some methods require the chemical treatment of the drop.

### I METHODS IN WHICH THE BLOOD IS DRAWN INTO CAPILLARY TUBES

1 *Vierordt's Method*—Vierordt allowed the blood to flow into capillary tubes, 1 mm in diameter and 5 cm long, until a column 5 mm long was obtained. A white horsehair, about 10 cm long, was introduced into each tube and drawn out slowly from time to time. It is not colored so long as the blood remains fluid. Coagulation begins when shreds of fibrin cling to the hair, and is completed when no more coagula are deposited on it.

2 *Koffman and Lidsky's Modification of Vierordt's Method*—Koffman and Lidsky made possible tests at a constant desired temperature. A coiled glass tube is passed through the cork into a horizontally placed thermoflask, filled with water of the desired temperature, usually 15°C. Extending into the glass tube through its cork, are a thermometer and a metal rod, to which are clamped in line small capillary tubes through which a horse-hair passes.



3 *Wright's Method*—Wright uses capillary tubes of equal length and caliber, the latter being about 0.25 mm. The finger is pricked and at quarter-minute or half-minute intervals a column of blood about 5 cm in length is aspirated into the tubes one at a time and drawn a little way up from the orifice. Two minutes after it is filled, the investigator blows down the first tube. If the blood cannot be dislodged, it is called "clotted", otherwise it is designated "liquid" or "clotting," as the case may be. The other tubes are then examined similarly, the time from the appearance of the drop on the finger until it blocks the tube being regarded as the clotting-time. To keep the tubes at a constant temperature of 37° C. or 18.5° C., they are, both before and after being filled with blood, placed with a thermometer in the pockets of a flannel bandage, which is fitted tightly about a tin can containing water kept at the necessary temperature, or they are immersed in a tumbler, or can, of water maintained at the desired temperature. In the latter instance rubber caps are fitted over the ends of the tubes before they are filled with blood. Either the finger is punctured but once, a ligature which has been placed about it being relaxed at frequent intervals, or a fresh prick is made for each tube.

4 *Fox's Modification of Wright's Method*—Hingston Fox obtains the blood as does Wright, but applies a rubber nipple to the tube and expresses the blood into water, regarding coagulation to have occurred when the blood no longer diffuses in the water but remains as a definite worm-like clot, or when the blood is expressed with difficulty. He keeps the tubes at room temperature and reduces his observations to a standard temperature of 60° F.

5 *McGowan's Method*—McGowan binds a rag tightly around a finger, ten seconds later pricks it, and, applying a capillary tube 6 inches long with a uniform bore of 1.5 mm., in ten seconds fills it for 4 inches in a continuous flow. The column of blood is then allowed to run down the tube and the end through which the blood entered is fused in a flame or is sealed with wax or paraffin. Care being taken not to hold the tube between the blood and the sealed end, the tube is laid down with a thermometer alongside, and at the end of each minute a file mark is made on the tube half an inch or less from the end of the column of blood that is remote from the sealed end of the tube. This piece of tube is then broken off, care being taken in breaking it to keep the two ends of glass approximated. The two ends of glass are then drawn apart, and the first stage of coagulation visible to the naked eye is shown by a minute shred of fibrin stretching between the two broken ends. When this is reached, the other parts of the tube are similarly broken to confirm the first observation.

6 *Addis's Modification of McGowan's Method*—Addis places McGowan's tubes in a glass cylinder which is placed in a metal cylinder covered with asbestos, the lid of which has three openings—one for the part containing the capillary tubes, one for a brass tube containing a thermometer, and one for a tube through which hot water is introduced so that both cylinders shall be filled with water maintained at a constant temperature of 20 C. He does not regard as indicating the end point of coagulation the fine filament of fibrin seen when the end of the tube is broken off, but regards rather the appearance of a thread of fibrin only in the last inch of blood. Addis takes the average of three tubes.

7 *Rudolf's Modification of McGowan's Method*—To heat the tubes at a constant temperature Rudolf employs a pint vacuum bottle, replacing its ordinary cork with a rubber one perforated in three places to accommodate a thermometer and two brass tubes, 7 inches long and just large enough in caliber to hold easily the glass blood tubes.

8 *Meier's Modification of McGowan's Method*—The bore of the capillary tube is immaterial in Meier's method, which otherwise is the same as McGowan's up to the point of filling the tube. Then, instead of sealing the end of the tube, Meier blows the drop at once onto a glass surface. Sealing the end of the tube he uses the sealed end as a rod to dip from time to time in the drop of blood, noting as coagulation the very definite moment at which the rod draws from the drop a fine thread of fibrin.

9 *Sabrazès' Method*—Sabrazès in 1899 devised a method which he perfected five and seven years afterward. His tubes, in which coagulation is determined in the same manner as in McGowan's method, are 5 cm long with an internal diameter of 1 mm. Three such tubes are filled with the second, third and fourth drops, respectively, that exude on a prick, so that the column of blood occupies about the middle of the tube. Sabrazès makes a file mark previous to the commencement of the experiment and as soon as he fills the tubes, places them in close proximity to the fine bulb of a special thermometer in the upper compartment of a glass box divided into two parts by a glass partition, the lower compartment containing hot water in winter and ice in summer, so as to keep the temperature at 18.5 C.

10 *Schultz's Method*—Schultz modifies the capillary tube by having one 4 inches long blown out into twelve or more regular expansions—tiny bulbs, or hollow beads—with short spaces between. The tube is filled with blood and at definite intervals the beads are broken off, one at a time, and shaken in a measured quantity of physiological salt solution. He designates as the end stage that point at which the bead remains filled with the clot and on shaking it only a very small quantity of red blood cells drops into the solution to color it.

## II METHODS IN WHICH THE CORPUSCLES ARE SET IN MOTION BY MEANS OF A CURRENT DIRECTED AGAINST A DROP OF BLOOD

1 *Brodie-Russell Method*—The Brodie-Russell instrument consists of a small, deep, circular air-chamber, closed below by a glass plate, on which lies a layer of water, and roofed in above by a metal ring, in which is fitted an inverted truncated glass cone. The air-chamber is surrounded by a water-jacket, which has inflow and outflow tubes, so that the temperature of the air-chamber can be regulated. The water-jacket is pierced by a metal tube, to the interior of which is fitted a glass tube, drawn out to a fine orifice which is directed toward the lower surface of the cone. A rubber bulb is attached to the outer end of this tube.

The glass cone is removed and its lower surface is dipped carefully into a drop of blood so that the whole of the surface is exactly wetted by the blood. The cone is then placed in position in the air-chamber, and by gently compressing the bulb a fine stream of air is thrown on the edge of the drop of blood, setting the corpuscles in motion. Coagulation has occurred when the movement ceases, as observed under the low power of the microscope.

2 *Pratt-Grutzner Modification*—Pratt and Grutzner omit the water-jacket and the truncated glass cone. They cement a metal ring, about 0.875 mm in height and 1.5 cm in diameter, to an ordinary glass slide. Through a hole in this ring is fastened a small metal tube (or hypodermic needle), to the outer end of which is attached a rubber bulb. A drop of blood is picked up on a heavy cover-slip, which is placed, with the blood downward, on the ring, the upper rim of which having been previously coated with petrolatum.

3 *Boggs' Modification*—Boggs also omitted the water-jacket but improved the glass cone. In his instrument the metal collar is pierced by a small hole, which allows an equalization of pressure in the chamber when the air is blown in. A few other slight alterations add to convenience in handling.

4 *Addis' Modification*—Addis substitutes for intermittent jets of air at unknown and variable temperature, a continuous stream of oil at a known and constant temperature. He uses Boggs's air chamber, which he keeps full of mineral oil. A stream of filtered oil from a reservoir is directed by the fine nozzle of the small tube tangentially against the edge of the drop. The oil in its passage from the reservoir passes in a flexible metal tube through a water-bath kept at a constant temperature by means of Schafer's gas thermometer, or, where gas is not available, by Gibson's electrical thermostat. Immediately after it has passed through the nozzle into the chamber and against the drop of blood, it impinges on the bulb of a fine thermometer and the temperature of the oil immediately surrounding the blood can be read off.

## III METHODS IN WHICH THE BLOOD IS PICKED UP IN A WIRE LOOP

1. *Biffi's Method*—Biffi's apparatus consists of a glass jar with a perforated cork containing a thermometer, with the reading above the cork, and a glass rod or tube into which is fused a platinum wire bent in such fashion as to have five loops of 3 to 4 mm diameter 1 cm apart. These loops are touched to the surface of a drop of blood so that each takes up a film of blood. The loops are then placed in the glass jar which is filled to a certain point with water at 20 to 25 C, the rod passing through the cork. At stated intervals the rod is pulled down so that one loop after another is introduced into the water. When coagulation is complete, the blood no longer diffuses into the water, leaving the loop perfectly clean, but remains unaffected as a solid red mass.

2. *Goldhorn's Modification of Biffi's Method*—Goldhorn made the loops more permanent by giving the wire an extra twist so as to have the loop unalterably fixed on a little stalk. He also made them larger.

3. *Buckmaster's Method*—Buckmaster makes an elliptical ring, about 6 to 9 mm in the long diameter and 4 inches in the short, of fine platinum, silver or iron. This loop is swept through a drop of blood without touching the skin. The loop is given a shake to detach some blood, leaving a thin film of even thickness. The loop is then placed in a small moist chamber, kept at a temperature of between 30 and 40 C, the shank of the loop being clamped in a holder so that it can be rotated. Commencing in a horizontal position, it is rotated at intervals into a vertical position and examined with a magnification of about ten diameters. When the corpuscles in the film no longer fall under the influence of gravity, leaving a clear space above, but the blood remains of the same opacity throughout, coagulation has occurred.

## IV METHODS IN WHICH THE BLOOD IS OBSERVED FOR THE APPEARANCE OF FIBRIN

1. *Simple Method with Slide and Needle, or Straw*—One of the simplest procedures for testing the clotting-time, which is still extensively employed, is mentioned by Murphy and Gould. A drop of blood is placed on a clean glass slide and its consistency is periodically tested by moving the drop with a needle. When the blood becomes gelatinous and fibrin shreds are thus demonstrable, coagulation has taken place. A similar method is described by da Costa. Several individual drops of blood of the same size are collected on the surface of a slightly warmed glass slide. At regular intervals of about one minute, a straw of a whisk-broom is lightly trailed through each drop in succession until sooner or later a delicate thread of fibrin may be observed clinging to the straw.

2. *Schwab's Method*—Schwab observed the appearance of fibrin threads in a hanging drop. He takes a small drop of blood on a cover-

glass and quickly places it face downward on a slide with a concavity. The appearance of fibrin threads in the clear serum at the periphery of the drop, as viewed under the oil immersion lens, indicates the occurrence of coagulation.

3 *Burker's Method*—Burker allows a drop of blood to fall into a drop of distilled water on a glass slide let into the lid of a box within which water is kept at a constant mean temperature of 18 C. Fine rods of glass are passed through the mixture of blood and water every half minute until a thread or a mass of fibrin is picked up.

4 *Riebes' Modification of Burker's Method*—Riebes uses a large glass slide with six concavities, which he fills with pure olive oil. One drop of blood is allowed to fall in each concavity and every half minute a fine wire, usually one used for cleaning hypodermic needles, is passed through one of the drops from below upward to the middle, so carefully that the drop is not subdivided. Throughout the test the slide is kept at a temperature of 20 C. Coagulation has occurred when a slight coagulum is raised over the level of the oil.

#### V METHOD EMPLOYING ACTIVATED SERUM

*Morawitz's Method*—The method described by Morawitz and by Birnbaum and Osten is based on the theory that blood-serum, made very active by the addition of caustic soda, can cause clotting in a fibrinogen solution. About 10 to 15 c c of blood are taken from a vein and kept cool in a beaker until the pressed-out serum settles. The latter is removed, centrifugated, and eventually filtered. To equal parts of this serum (5 c c) the same amount of a decinormal solution of sodium hydrate is added and after a quarter of an hour's action the lye is neutralized with decinormal sodium chlorid. Two c c of a clear and opalescent solution of fibrinogen, obtained from horse's blood, are placed in a test-tube, and with a pipette several drops—5 to 30—of the activated serum are added. The solution, at first fluid, gradually takes on an oily nature, and finally becomes gelatinized. The end point of clotting is the moment when the fluid surface begins to be uneven in the tilted test-tube.

#### VI METHOD EMPLOYING ANTICOAGULANT SUBSTANCE

*Chantemesse's Method*—Chantemesse mixes a minute volume of blood with the same volume of a solution of some salt preventing coagulation. To suppress coagulation of normal blood *in vitro* it is mixed with an aqueous 1 to 800 solution of potassium oxalate. When the coagulating force is greater, a stronger solution of oxalate is needed to oppose the formation of a clot, when the force is weaker, a weaker solution suffices. Several samples of blood are mixed with oxalate solutions of different strengths, 1-400, 1-600, 1-800, 1-1000, 1-1200, 1-1500, 1-1800, the mix-

ture being received and preserved in fine pipettes, like Wight's, and at the end of an hour a glance at the pipettes shows whether the coagulability is equal to, or greater, or less than normal

#### VII METHOD WHICH MEASURES THE MECHANICAL RESISTANCE OF COAGULATING BLOOD

*Koffman's Coagulo-Viscosimeter.*—Koffman devised an intricate apparatus in which the blood is received in a nickel vessel with an internal diameter of 1 cm which is rotated in a water-bath by means of a clock-motor so that it makes twelve to fifteen turns per minute, projecting down into the middle of the vessel is a small silver blade fastened to a shaft, the upper end of which is connected with a pointer on a dial with 100 divisions. One end of a fine mainspring is attached to this shaft, the other end being fixed. This prevents the free rotation of the blade with the blood in the vessel and permits only a certain amount of turning. The amount of turning for the time being is proportional to the degree of coagulation of the blood examined and is easily read on the dial. A curve is made, the height representing the degree of turning and the base the number of minutes from the moment of puncture.

#### VIII METHODS DEPENDING ON CHANGES IN THE CONTOUR OF THE BLOOD

1 *Hayem's Method*—In Hayem's method, as described more fully by Bezançon and Labbé, a flat-bottomed glass test-tube, about 5 cm high, with an interior diameter of 7 mm, is filled to a height of 3 to 4 cm with blood as it flows from the wound. The tube is tilted at intervals, coagulation being completed when the blood becomes so solid that the level no longer changes with each movement of the tube.

2 *Milhan's Method*—In Milhan's method a rather large drop of blood is allowed to fall on a glass slide, which at intervals is carefully tipped vertically. Coagulation has occurred when the drop, instead of becoming tear-shaped on tilting the slide, does not change its shape, but remains convex in outline.

3 *Bezançon and Labbé's Modification of Milhan's Method*—Bezançon and Labbé let three drops of blood fall on three slides which they place under a bell-jar and examine from time to time by tilting.

4 *Hinman and Sladen's Modification of Milhan's Method*—Hinman and Sladen pick up a series of drops by touching a slide to the drops and, placing the slide on a millimeter rule, wipe off all drops whose diameters are less than 4 mm or greater than 5 mm. On tilting the slide, they observe not only the contour of the drop but also the changes in density when held to transmitted light, the dense portion being in the center when coagulation has occurred and at the lower edge when the drop is still fluid.

5 *Schwarz and Ottenberg's Modification of Milhan's Method*—Schwarz and Ottenberg take a drop of blood, 5 mm in diameter, from a prick in the finger, on a cover-slip, which they invert on a hollow ground slide and ring with liquid petrolatum to prevent evaporation and exclude air currents. They determine the moment of coagulation by the failure of the drop to sag when the slide is tilted. In a personal communication a couple of years ago Dr W M L Coplin described to me a similar method he has used.

6 *Duke's Modification of Milhan's Method*—Duke's apparatus consists of a glass slide on which are mounted two 5 mm disks. On one disk is placed a drop of the blood to be tested and on the other a drop of normal blood, the two drops being of about the same depth. The slide is then inverted over a tumbler nearly full of water kept at 40 C and is covered with a warm damp cloth. When tested by tilting the cloth is removed and the slide taken up from the tumbler.

7 *Author's Modification of Milhan's Method*—Instead of a slide I use the lid of a German stender-dish, which I cover with the dish as soon as the drops are obtained. I measure the drops while covered and regard only the drops of proper size. Before the finger is punctured, and immediately after the drops are measured, the dish is placed in a pan of water, which is maintained at a constant temperature of 37 C. As the majority of my tests mentioned in this paper were made with this method I shall describe it in detail.

My coagulometer consists of a German stender-dish, 80 mm in diameter and 40 mm high, a pan big enough to hold the dish and fitted with an outlet tube and a bracket for supporting a thermometer, an ordinary bath-thermometer, a broad elastic band, a piece of rubber tubing, a clamp and a millimeter rule. I use an oval zinc pan, with perpendicular sides. As zinc is not acted on by water, it is preferred to tin, which rusts, and to copper, which turns green. (An ordinary five-cent tin baking-pan will answer, however, with an outlet and a bracket which a tinsmith will put in for ten cents.) The rubber tubing is attached to the outlet tube and clamped.

In employing this method, the under surface of the lid of the stender-dish is thoroughly cleansed with soap and water and then with alcohol, and dried. The rim of the dish is smeared with hydrated wool fat (lanolin) or petrolatum. The lid is then adjusted and held in place by the rubber band. The pan, with the thermometer in place, is partially filled with water of a temperature of 37 C (98 F), that temperature being maintained by the addition of hot or cold water. Any excess of water is allowed to escape through the outlet. The dish is placed in the pan of water with the lid undermost.

The patient's finger is thoroughly cleansed with soap and water and with alcohol, and dried. The stender-dish is taken from the water and rapidly dried, and the elastic band is removed. A deep puncture with a sharp, lance-pointed instrument is made in the finger so that the blood flows freely without undue pressure. The first drop is wiped off and note is made of the exact time the second drop appears. When this drop reaches sufficient size it is touched to the uppermost surface of the inverted lid of the stender-dish, which is held horizontally, and deposited on it. The finger is again wiped off and several other drops are deposited similarly, the time of the appearance of each being noted. I usually take four drops, placing one in each quadrant, and mark the top of the lid with a pen or paraffin pencil. The dish is then placed on the lid and the diameter of the drops measured by passing the rule beneath the lid. It is best to disregard all drops whose diameters measure less than 5 mm or more than 8 mm. The rubber band is reapplied and the inverted dish is again placed in the water-bath.

At intervals the dish is removed from the water and tilted. At first this must be done cautiously to avoid the drops running, later the dish can be held vertically. The contour of the drop is observed from the side and the density is observed on full view. If, when seen from the side, the drop sags, becoming tear- or pear-shaped, or if, on holding the dish to transmitted light and looking at the face of the drop, it appears dense below and clearer above, complete coagulation has not occurred. But when the profile of the drop does not change when the dish is tipped vertically, but remains convex, and when the full view shows the density in the center or evenly distributed, the blood has fully clotted. To confirm this, the clot should be picked up or moved. Note is taken of the time at which this change occurs in each drop. The interval between the moment the drop appears on the finger and the moment it is completely coagulated is taken as the clotting time.

Twenty normal persons examined according to this method gave an average clotting-time of eight and two-thirds minutes with limits of twelve and one-quarter and four minutes.

## 2 CLOTTING-TIMES ACCORDING TO THE DIFFERENT METHODS

The length of time it takes a drop of blood to coagulate varies with the method employed for measuring it. In referring to a clotting-time, therefore, it is necessary to mention by what method it was obtained. The multiplicity of coagulometers, and hence of coagulation times, renders difficult any exact comparisons of results obtained by different observers.



## I THE NORMAL CLOTTING-TIMES ACCORDING TO THE DIFFERENT METHODS

In the following table are given the normal clotting-times obtained with the different methods by their originators. It will be seen that the greatest variations occur. There is practically no such thing as an absolutely normal clotting-time. In the same patient at the same time two minutes and twenty minutes may be the normal clotting-time, depending on the method employed.

TABLE 1—NORMAL CLOTTING-TIMES OBTAINED WITH DIFFERENT METHODS

Method Employed	Clotting Time Obtained
Vierordt's	9½ minutes
Wright's	2½ or 5 minutes
McGowan's	8 minutes
Addis' modification of McGowan's	9½ minutes
Rudolf's modification of McGowan's	8½ minutes
Sabrazés'	9 to 10 minutes
Schultz's	5 minutes
Brodie-Russell	3 to 8 minutes
Pratt-Grutzner modification of Brodie-Russell	3 to 8 minutes
Bogg's modification of Brodie-Russell	3 to 8 minutes
Addis' modification of Brodie-Russell	8 minutes
Biffi's	7 to 10 minutes
Goldhorn's modification of Biffi's	about twice as long as above
Buckmaster's	5¾ minutes
Slide and Straw	2½ to 5 minutes
Schwab's	4¾ to 5½ minutes
Burker's	6 to 7 minutes
Riebe's modification of Burker's	12 to 14 minutes
Morawitz's	5 minutes
Hayem's	3 to 20 minutes
Milian's	15 to 34 minutes
Bezangon & Labbé's modification of Milian's	10 minutes
Hinman & Sladen's modification of Milian's	5 to 8 minutes
Duke's modification of Milian's	5 to 7 minutes
Author's modification of Milian's	8⅓ minutes

## II DEVICES FOR COMPARING PATHOLOGICAL CLOTTING-TIMES OBTAINED BY DIFFERENT METHODS

Owing to the wide variations in the normal clotting-times obtained with the different instruments, it is practically impossible to compare pathological records. This lack of uniformity is most unfortunate, as it prevents investigators from confirming each other's work. In order to overcome this difficulty I have devised two methods of comparing records taken with different instruments. With each apparatus one definite time must be taken as the normal. Where two figures are given, the mean should be taken.

1 *Expressing the Pathological Clotting-Time in Terms of the Normal*—The clotting-time in a given disease may be expressed in terms of the normal by means of a fraction whose denominator is the normal time and whose numerator is the abnormal time, or this same fraction may be expressed as a decimal or as a percentage. Thus, if the normal clotting-

time obtained with one instrument is eight minutes and in a certain disease the clotting-time is six minutes, this latter may be expressed as 6-8, or 0.75, or 75 per cent of the normal

*2 Reducing the Clotting-Time Obtained with One Method to the Terms of Another Method*—Another method of comparing records taken with different instruments is to reduce one to the terms of the other by means of proportion, i. e., the normal time of method A is to the normal time of method B, as the clotting-time in a certain disease taken with method A is to X, which is the abnormal time obtained by the A method expressed in terms of the B method. Thus, the abnormal time, six minutes, just referred to, would be expressed in terms of a method that gives the normal clotting-time as four minutes, by means of the following proportion

Eight min (normal time of first method)    4 min (normal time of second method)  
 6 min (pathol time according to first method)    X=3 minutes  
 (pathol time expressed in terms of second method)

### 3 FACTORS AFFECTING THE CLOTTING-TIME OF SHED BLOOD

The great variations in the clotting-time found by different observers, and even by the same observer, are doubtless due to factors of two kinds intrinsic factors affecting the blood itself while still in the vessels, and extrinsic factors, affecting the blood after it has left the vessels<sup>1</sup>

Of the factors affecting the clotting-time of shed blood, some doubtless have to do with the manner in which the blood is drawn, while others are connected with the method employed for measuring the clotting-time

#### I SOURCES OF ERROR IN THE METHOD EMPLOYED FOR MEASURING THE CLOTTING-TIME

The methods employed for measuring the clotting-time often themselves contain many sources of error. Some coagulometers are devised particularly to avoid certain of these factors. Undoubtedly there are causes of error that now are not even recognized

*1 Contact with Foreign Body*—Contact of the blood with anything except the intact endothelial lining of the vessel, oil, petrolatum or paraffin, shortens the clotting-time, the degree depending on the character and the size of the contact surface. Blood which Freund found to remain liquid when received in a greased vessel clotted when an ungreaed glass rod was brought in contact with it. A portion of this blood, however, clotted in a few minutes when placed in an ungreaed dish

<sup>1</sup> The writer in September, 1908, presented a paper before the Medical Society of the State of Pennsylvania in which a number of these factors are described Solis-Cohen, Myer Factors Influencing the Coagulation Time of the Blood, Penn State Med Jour, 1909, xii, 953

Addis made several tests showing the coagulation time to be seventy to eighty minutes when the blood was not in contact with a foreign body, twenty to twenty-six minutes when in contact with glass alone, ten to sixteen minutes when air was the only foreign body, and five minutes when the blood was exposed to both glass and air

It is generally believed that uneven surfaces accelerate coagulation more than a surface of uniform character, such as smooth glass, and that with the latter contact surface, the greater its extent, the more rapidly coagulation occurs. That other factors may enter here is seen from the experiments of Bouchard, who demonstrated that when blood is received in a capillary tube, the portion of blood that enters the tube last coagulates more quickly than normal, while that portion that enters first clots more slowly than normal, this retardation being the greater, the longer the column of blood and consequently the greater the contact surface. It seems to him as if, in flowing through the tube, the blood divests itself of that which normally provokes coagulation, and as if that something accumulates in the first portion of the tube.

Whatever the amount of error due to contact with foreign bodies, it should always be constant in a given coagulometer. In each observation the blood should be in contact with exactly the same amount and kind of foreign body.

Capillary tubes offer the largest extent of contact surface. Vierordt's, Fox's and Koffmann's methods introduce second contact surfaces, a horse's hair in the first, water in the second, and the silver blade in the third. There are three foreign bodies in Mercier's method—the tube, the glass surface, and the rod, and two in Burkner's method—the water and the glass rod. McGowan breaks off the end of the tube containing the blood which entered first and consequently clots last, and then goes toward the portion which entered last and clots first. Sabrazès lessens this source of error by using a short tube, while Addis avoids it altogether by regarding only the last inch of blood.

In Hayem's method the extent of contact surface is large and, besides, many drops fall on the sides of the test-tube. The needle, or straw, and slide introduce two foreign bodies into the method employing them. Wire loops present an uneven surface, Goldhorn notes that in Biffi's instrument the blood goes by capillarity to the point where the two wires cross. The contact surface is smallest in the Brodie-Russell method and its modifications, in Milhan's method and its modifications, and in Schwab's hanging drop.

2 *Dirt*—The clotting-time is affected by the presence of dirt, no matter how minute, on the contact surfaces and on the finger. Absolute cleanliness of skin and instruments is essential.

Capillary tubes, especially if beaded, and wire loops are not so easily cleansed as are glass slides, the lid of a stender-dish, and the smooth surface of a glass cone

*3 Size and Shape of Drop*—Hartman, Bezangon and Labbé, and Hinman and Sladen believe that the size of the drop has some influence on the clotting-time, but Buiker thinks not. Addis states that if the margin of the drop does not come absolutely up to the edge of the surface of the cone of the Biedie-Russell instrument, the stream of oil will not affect it in quite the same way, again, that the drop is then not always circular in outline, and the flow of corpuscles is liable thereby to be slightly obstructed

In my method I found that the size of the diameter of the drop affects the coagulation time very little, provided it is not less than 4 mm or greater than 7 mm. Often the clotting-time was the same in drops whose diameter measured 4 mm at one extreme and 8 or 9 mm at the other, obtained from the same puncture and examined at the same time

The diameter of the drop is uniform in size in Hinman and Sladen's, Schwalz and Ottenberg's, Duke's, and my modifications of Milian's method

It must be borne in mind, however, that the diameter of a drop is not always an accurate index to the amount of blood contained in the drop. The height must also be taken into account

In thirty-five cases (of tuberculosis) where the drops were high, the average coagulation-time was five and three-quarter minutes. In fifteen tests with shallow drops the average time was only four minutes. According to Duke, also, a very shallow drop clots one to two minutes sooner than a very deep one

There seems to be some relation between the size of the drop and the viscosity of the blood. This may be due to the fact that the viscid drops are always high, while, on the other hand, when the viscosity is low, the drop tends to spread and thereby becomes shallow. On this account my drops of large diameter were usually very shallow. The longer clotting-time of high drops may, however, also be explained by their increased viscosity

I always endeavored to obtain high drops

The difference that others have noticed in the clotting-time of drops of different sizes may be in part a result of the quicker evaporation of the smaller drops, while the fact that drying is less likely to occur when the drops are protected by the stender-dish, may account for my results

Another factor, related to the height of the drop, demonstrates the importance of viewing the drop from the front as well as from the side, when examining drops according to Milian's method or one of its modifications. A high drop ceases to change its shape when tilted and

observed from the side before the density ceases to change when the tilted drop is looked at in front. The reverse is true of shallow drops.

4 *Amount of Blood Withdrawn*—As will be shown later, there is a tendency for the coagulation-time of the blood to diminish during and after a hemorrhage. It is important therefore not to withdraw enough blood to produce this reaction. The methods that use but a few drops of blood seem to me preferable. Hayem's method of filling a test-tube with blood is therefore not a fair test. This progressive diminution of the clotting-time is fairly rapid. In one of Addis' cases, the first blood from the wound clotted in seven and one-quarter minutes, that obtained after one minute in five and one-quarter minutes, and blood flowing after two minutes in three and three-quarter minutes. The blood introduced in the last of a series of capillary tubes would therefore coagulate more quickly than the blood in the first tubes. Even in a small capillary hemorrhage of a few drops there seems to be a slight difference in the coagulability of the different drops. In my tests with my method each drop clotted about one-eighth or one-quarter of a minute quicker than the drop immediately preceding. This of course may have been more apparent than real. It merely means that the moment coagulation was noted as being complete all the four drops were usually well clotted, although they had been obtained one-eighth or one-quarter of a minute apart. It is no doubt possible that in some instances the exact moment in which clotting occurred in each drop was not immediately noted, as the drops were observed only at intervals. In many cases, however, the drops were examined at the very instant coagulation was taking place.

5 *Mechanical Disturbance of the Blood*—It is probable that coagulation is hastened by any disturbance of the blood, such as pulling a horsehair through it, as in Vierordt's method, or trailing a needle, wire, glass rod, or straw, through it, as in several methods, or tilting the drop, as in Hayem's, Buckmaster's, and Milian's method and its modifications, or setting it in motion by a current of air or oil, as in the Brodie-Russell instrument and its modifications, or in whirling it against a blade, as in Koffmann's coagulo-viscosimeter.

6 *Evaporation*—Milian has shown that evaporation, by diminishing the quantity of water in the blood, accelerates coagulation. Hence currents of air interfere with the test.

In the first tests I made with the uncovered slide, according to Milian's method, the evaporation of the blood was quite marked, by the time coagulation was complete, the drops were dried about the edge for a third of their diameters. My recent comparative tests made simultaneously with covered and uncovered drops of blood from the same person would seem to indicate some relationship between evaporation and the

humidity of the air In blood exposed to the air, coagulation was seven-eighths of a minute longer when the humidity was 75 or above than when it was below 75

In Milian's method, as well as in Hinman and Sladen's modification of it and in the methods in which one drop or several drops of blood are collected on a slide and tested with a needle, wire, or straw, the blood is exposed to the air and consequently to evaporation Those methods therefore can be used only in a closed room In Bezançon and Labbé's and Duke's modifications of Milian's method the slide is exposed to the air whenever it is examined The thin film used by Buckmaster and Biffi surely must have a tendency to evaporate Air is definitely blown on the drop of blood in the Brodie-Russell apparatus and in the Pratt-Grutzner and Boggs modifications of it, the force and frequency of this disturbing feature naturally varying with the operator The blood is protected from drafts in Schwarz and Ottenberg's and my modifications of Milian's method and in the methods employing capillary tubes, which therefore can be used in a ventilated ward, or in the open air in the case of consumptive or pneumonia patients

7 *The Temperature*—Pratt, Murphy and Gould, McGowan, and Hinman and Sladen are of the opinion that coagulation is not appreciably affected by moderate variations in the temperature, but present no experimental proof of this assumption Milian, Burke, Bezançon and Labbé, Goldhorn, Denk and Hellman, Weil, and Jaequot, on the other hand, assert that heat accelerates coagulation, while cold retards it This action has definitely been shown experimentally to be a fact by Addis, Brodie and Russell, Fox, Hartman, Rudolf, Wright and myself

Wright found the clotting-time to be two to four minutes when his tubes were kept at 18.5 C, and one minute and thirty-five seconds to two minutes and ten seconds when the water registered 37 C Brodie and Russell obtained a clotting-time of eight and eight and a quarter minutes when the water in the instrument was 20 C, and three to four minutes with a temperature of 30 C Rudolf's figures show that, roughly speaking, each degree between 15 and 20 C of the temperature at which the test is carried out makes a difference of about one minute in the coagulation-time

Addis constructed a chart showing a regular decrease in the clotting-time from two and one-half minutes at 10.25 C to five and one-half minutes at 20.5 C This writer regards as practically worthless methods where no attention is paid to differences of temperature He believes the extraordinary variations in coagulation-times obtained by use of these methods to be to a great extent due to variations of the temperature

My own experiments also demonstrate that temperature does exert an influence Five comparative tests were made at the same time with blood

from the same persons, kept both at 37° C and at 18.5° C. The average clotting-time in four of these cases was six and three-quarter minutes at the higher temperature and eight and one-quarter minutes at the lower. The fifth case gave a clotting-time of eight and one-quarter minutes at 37° C and of twenty and three-quarter minutes at 18.5° C, the latter probably being a result of the condensation of moisture on the inside of the dish.

A series of observations was also made on blood from the same persons tested both with the author's method at a temperature of 98° F and on an uncovered glass slide at room temperature. Five subjects were tested when the room temperature was 75° F and above, and twelve subjects were tested when the room temperature was below 75° F, with the results shown in Table 2.

TABLE 2—INFLUENCE OF TEMPERATURE ON THE CLOTTING-TIME

	Blood from the Same Persons Tested Simultaneously			
	Writer's Method at 98° F	Milhan's Method at 75° F and above	Writer's Method at 98° F	Milhan's Method at a Temp. Below 75° F
Number of cases	5	5	12	12
Aver. Clotting Time	9 $\frac{3}{8}$ '	9 $\frac{3}{4}$ '	9 $\frac{1}{2}$ '	10 $\frac{1}{2}$ '
Max. Clotting Time	10 $\frac{1}{4}$ '	11 $\frac{3}{8}$ '	12 $\frac{1}{4}$ '	14 $\frac{1}{4}$ '
Min. Clotting Time	8 $\frac{1}{4}$ '	6 $\frac{5}{8}$ '	3 $\frac{1}{4}$ '	3'

Blood kept at 98° F therefore took five-eighths of a minute longer to clot than blood exposed to a room temperature of 75° F or more, but one and three-tenths minutes less than blood exposed to a room temperature below 75° F.

On hot days, in order to keep the water in the pan at 18.5° C, ice-water had to be added continually. In such cases there was always a little moisture condensed on the top or sides of the dish, and on very hot days so great a condensation appeared on the lid that it constituted an additional element of error. When, for instance, the room temperature was 90° F, drops on an uncovered slide clotted in less than eight minutes, and those in a stender-dish kept at 37° C (98° F) coagulated in eight and one-quarter minutes, but it was twenty and three-quarter minutes before clotting occurred in the drops that were tested in a stender-dish at a temperature of 18.5° C (66° F).

There is no doubt that the adhesion of the blood to the glass contact surface is affected by temperature. Whenever the glass is not heated to 98° there is a great tendency for the drop to run when tilted. The blood adheres much better when the glass surface is kept at the higher temperature.

A drop tends to spread when deposited on a cool glass surface, and, being shallow, elots more quickly than a similar drop deposited on a warm surface, where it remains high .

Coagulometers that seem to keep the blood at a constant temperature vary in the thoroughness with which they accomplish this Denk and Hellman point out an error in the gauge of the capillary tubes, stating that the thickness of the glass affects the rapidity of warming and emphasizing the need of very thin tubes According to this, Wright's home-made tubes are more accurate than those supplied by the instrument-maker. The stender-dish I use is of rather thick glass

In Sabrazès' method, in Addis' modification of McGowan's method, and in my own method the tube or dish containing the blood is removed from the water to be tested, during which time its temperature tends to approximate the room temperature Addis has recently stated that further experience with his modification of McGowan's method has shown that the results cannot be relied on if the room temperature is above 20 C (68 F). Coagulation-times taken on hot summer days when the temperature in the ward was above 20 C were found to be shorter than normal, although the temperature within the apparatus was kept at 20 C The higher temperature outside, according to Addis, must therefore have accelerated the coagulation, although it had an opportunity to act only during the relatively short time during which the tubes were removed from the apparatus for examination A large part of the difference in the coagulation times of people in health, he thinks, was no doubt due to this cause

Addis found it impossible to maintain a constant temperature in Brodie-Russell's, Burker's, and Buckmaster's instruments There seems to be little doubt that Addis' modification of the Brodie-Russell instrument and Wright's coagulometer maintain an uninterrupted constant temperature

*8 Dilution of the Drop*—Burker states that the dilution of drops of blood had no influence on the coagulation-time Stodel, however, demonstrated that blood diluted with a solution of sodium chlorid 9 to 1,000 coagulated more slowly than pure blood, and also that the greater the dilution the more slowly coagulation occurred

*9 End-Point Adopted*—The end-point adopted in the different methods as indicating that coagulation has occurred is not always accurate, clear and definite The methods employing capillary tubes, as well as those in which the blood is watched for the appearance of fibrin threads, have practically the same end-point. According to the investigations of Addis, Buckmaster, Fox, and others, this is not sure proof that coagulation has occurred in the whole drop, as a thread of fibrin several millimeters long can often be demonstrated ten seconds after the blood has



been drawn, when the blood is touched with a needle or with a glass surface. In such a case there are no other signs of coagulation and the same drop may give a coagulation time of seven or eight minutes. The conditions under which this phenomenon occurs are present when the blood is blown out of one of Wright's tubes and the tube is slowly withdrawn from the drop, and are always present in Meicler's method.

Those methods having as an end-point a loss in fluidity, as Hayem's, Brodie and Russell's and its modifications, Milhan's and its modifications, and Buckmaster's, are subject to a source of error in that the change in the physical character of the blood may be due to agglutination of the corpuscles.

In Brodie and Russell's method and its modifications the end-point is not always the same in the hands of different observers. Addis mentions three possible stages, sixty and fifty seconds apart, which might be adopted as indicating coagulation. Hinman and Sladen divide into four stages the changes in the movement of the red corpuscles set up by the blowing. They believe that Pratt and Murphy and Gould adopted as an end-point the stage they label C, while Brodie and Russell used stage D, the stage Hinman and Sladen finally used themselves.

*10 Personal Equation*—I regard the personal equation as a very important factor. To it I attribute largely the fairly constant results obtained by each investigator with the instrument he has devised or is accustomed to, when others obtain discordant results with the same method. Whatever the factors of error, they usually remain about the same when the test is always performed in exactly the same manner. Familiarity with a method and facility in its employment even lessen the effects of sources of error connected with it. In Milhan's method and its modifications, for instance, that man will disturb the drop least who needs to tilt the drop least often and who can observe its shape most quickly. As already mentioned, the determination of the end-point in several of the methods, particularly Brodie and Russell's, is often a matter of personal equation. In the latter method the force and frequency with which the bulb is compressed, affecting two factors—the draft of air and the mechanical disturbance of the drop, depend on the individual compressing it. The manner of obtaining the drop of blood and the rapidity with which it is transferred to the apparatus undoubtedly varies with different workers.

Complicated methods, and those requiring technical skill, experience, and powers of observation of a high order, are most likely to be affected by the personal equation. A coagulometer, to be reliable, must give the same kind of results in everyone's hands.

*11 Unrecognized Causes of Error*—There are many sources of error not recognized at present. These probably explain the curious results

that are sometimes encountered. The coagulometers that always give constant results under the same circumstances are probably freest from the unrecognized factors of error.

With my method results are fairly constant. Four drops taken in succession from the same puncture usually coagulate in about the same periods of time. The results obtained from two different punctures, made fifteen to thirty minutes apart, are as a rule fairly constant. This probably means that unrecognized sources of error have been reduced to a minimum.

Hayem's method gave unsatisfactory and discordant results in his own hands, the time varying greatly in one and the same animal.

My own results with Wright's tubes were unsatisfactory. It was often my experience that the blood in eight tubes filled from the same puncture did not coagulate in equal periods of time. Wright's method proved unsatisfactory in Brodie and Russell's hands, successive observations taken at intervals of five to ten minutes not giving concordant results. In the hands of Murphy and Gould it failed to give results in 15 per cent of the observations. In a certain number of cases the blood would not adhere to the lumen of the tube, a fact they were unable to explain. They found in blood from healthy subjects variations between one and seven minutes, which extremes they attribute to technical errors. Turner, using Wright's tubes, often found a difference of over two minutes in the blood from three successive pricks in the same individual on different fingers; on only three occasions in over 1,000 observations did he find the same coagulation rate in the blood from three consecutive pricks. In nearly 50 per cent of the forty-three estimations made by Addis with Wright's tubes, only an approximate time could be arrived at, because coagulation occurred in one tube although it was not present in others until later.

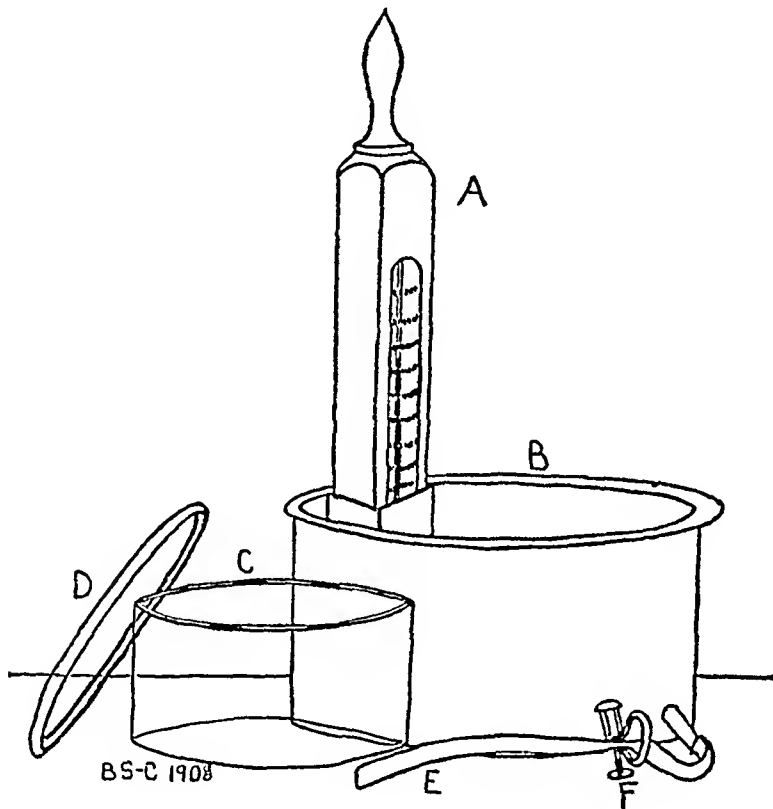
The Brodie-Russell instrument failed in less than 5 per cent of the observations in Murphy and Gould's hands, but it gave variations in blood from healthy subjects between one and seven minutes. Pratt noted extraordinary variations in the coagulation-time taken with his modification of this instrument, the time in one case varying from two to nine and one-half minutes within half an hour. Addis in over 200 estimations with Pratt's or Bogg's modification of the Brodie-Russell coagulometer, found that with its use the time varied considerably in consecutive observations on the same person, a time of four minutes being followed by one of twelve minutes, and so on, without any regularity.

Bezangon and Labbé found inexplicable variations in their modification of Milian's method, sometimes the first drop, sometimes the last drop coagulating most quickly. Hinman and Sladen found their modification of Milian's method to be thoroughly reliable. In my hands also it has given satisfactory results.

## II COMPARISON OF THE DIFFERENT COAGULOMETERS

The methods of measuring the coagulation time that are freest from sources of error are Addis' modification of Brodie and Russell's method and my modification of Milhan's method. The former is probably the most accurate of all, but is too intricate and cumbersome for general application, being fitted chiefly for laboratory use.

My coagulometer seems to me to combine simplicity with accuracy. It can be made and used by any physician and is easily carried about. At the same time it presents a contact surface limited in extent, clean, and uniform in character, maintains a fairly definite and constant tem-



Author's Coagulometer, A, ordinary bath thermometer, B, zinc pan (common tin pan will answer), C, German stender-dish, D, lid of German stender dish, E, rubber tube, F, clamp

perature, prevents evaporation, provides for drops of uniform size, largely eliminates the personal equation, and presents fairly constant results.

While less accurate than the above, Milhan's method is the simplest of all, requiring merely a plain glass slide. It is always available and as a rough test is to be recommended.

## III FACTORS DEPENDING ON THE MANNER THE BLOOD IS DRAWN

There are some conditions affecting the coagulation of shed blood which are not produced by the instruments used but have to do with the manner in which the blood is drawn.

1 *The Part Punctured*—Murphy and Gould found no marked difference between the coagulation times of blood drops taken from different points on the surface of the body, provided the flow had been equally free. It was Piatt's experience also that there were no characteristic differences in the coagulation time dependent on the part examined, although he remarks that blood from different parts of the same individual, examined at the same time, showed striking differences in the coagulation time. Hayem, on the other hand, using his own method in simultaneous observations, obtained clotting-times of nine minutes in blood from the ear and two minutes in blood from the thigh.

2 *Contact with the Tissues*—That contact with the tissues shortens the clotting-time has been noted by many observers, some of whom variously attribute this influence specifically to the wound, the blood, lymph, and the skin.

It is the coagulant action of the tissues which, according to Delezenne, causes immediate clotting of blood at the surface of the wound. Spangaro also has shown that blood taken directly from a vessel takes a much longer time to clot than when it first comes in contact with the tissues. Coagulation was equally hastened when a small portion of muscle or glandular tissue was introduced into the tube where the blood was received directly from the vessel or when the sides of the tube were merely rubbed with the tissues.

A *Influence of the Wound* Delezenne showed that bird's blood clots in half a minute to two minutes when allowed to come in contact with the wound, but remains unclotted for two to eight days when drawn directly from the vessel through a glass tube.

Arthus showed in dogs that the coagulation of blood flowing on the wound was always more rapid than that of blood received in a tube—forty seconds, for example, instead of three minutes. By allowing a 1 to 100 sodium chlorid solution to fall drop by drop on the surface of an exsanguinated cutaneous wound he obtained a saline lavage water capable of hastening coagulation of the blood. Making the lavage water flow over the wound several times in succession increased its coagulating power.

Milian and Addis believe that fibrin ferment quickly forms and collects around the lips of the wound, and tends to shorten the coagulation-time of the blood which follows. Spangaro states that when a portion of tissue is placed in blood obtained without contact with the tissues coagulation is not so rapid as when the blood comes in direct contact with the wound.

Mellanby gives a detailed theoretical explanation, stating that when a blood-vessel is so injured that blood may escape from it, the injured vessel-wall or the surrounding tissues liberate kinase. This kinase enters

into the blood and there finds all the necessary factors for the production of fibrin ferment—prothrombin and calcium salts. Fibrin ferment is therefore formed and since the association of the prothrombin with the fibrinogen entails that the ferment produced is in molecular proximity to the fibrinogen, coagulation of the fibrinogen ensues in the shortest possible time.

Bernheim very recently demonstrated experimentally that in the blood-vessel wall itself there is a substance which, once the vessel is injured, probably aids in the formation of a clot.

**B Contact with Blood** When the drop to be tested comes in contact with recently shed blood a very marked diminution in the clotting-time results. Addis attributes this to the addition to freshly issuing blood of preformed fibrin ferment. Spangaro has shown that contaminating the sides of a tube with blood hastens the coagulation of blood that is received into it without having come into contact with the tissues.

In drawing blood for testing, therefore, it is absolutely essential that all trace of one drop be removed before the next appears.

**C Contact with Lymph** Wright pointed out the influence of lymph in decreasing the clotting-time, as shown by the admixture of blood to fresh lymph, muscle juice, and blister fluid. The acceleration of coagulation when pressure is made on the tissues he attributes to the driving of lymph into a bleeding wound, and contrasts the short coagulation-time of the "mixture of blood and lymph obtained from a small occluded puncture on the finger" with the much longer coagulation-time of the blood issuing spontaneously from a free puncture. The effects of the wound and of blood he believes to be due to the admixture of lymph contained by blood leaving a wound.

Pratt has found that an increased amount of lymph in the tissues does not accelerate the coagulation-time, blood from very edematous tissues not coagulating more rapidly than blood from non-edematous parts of the body.

**D Influence of the Skin** Milian believes that there exist in the skin substances that accelerate coagulation. Hinman and Sladen found that the longer a drop is in contact with the skin surface, the more rapidly it clots when transferred to the instrument, each second of contact added shortening the coagulation-time by minutes. They also state that the more rough and scaly the skin, the quicker is the normal clotting. Addis compared the coagulation-time taken when the blood was protected from contact with the skin by smearing the surface with hydrated wool fat (lanolin) before the puncture was made, with the time taken in the ordinary way. This showed that contact with the skin for the short period which elapses before the blood can be introduced into the apparatus has no appreciable effect.

It is quite possible (if not probable) that the influence supposed to be exerted on the clotting-time by contact with the wound, the skin, blood and lymph, are all due to one and the same factor, the action of fibrin ferment which, as Mellanby has stated, does not circulate in the blood, but is produced when any tissue is injured so as to liberate thrombokinase in the blood-stream

3 *Depth and Character of the Wound*—Piatt found the clotting-time to be influenced by the depth and extent of the cut. If a large, deep cut were made, from which the blood flowed freely, the coagulation-time was relatively slow, while blood from a small superficial cut coagulated quickly. In one case, for instance, blood from a superficial cut of the skin coagulated in two minutes, while blood from a deep cut in the same individual coagulated in seven minutes. Murphy and Gould furnish an explanation of this phenomenon, stating that if the needle-prick is deep, the rapid flow of blood will wash away the ferment and prevent immediate coagulation, while the reverse is true of a superficial prick. They regard it as obvious that the prick should be deep enough to cause a free flow of blood. The accelerated coagulation of blood from a superficial puncture Hinman and Sladen attribute to the longer contact of the blood with the skin, owing to its slow and scanty flow.

On the other hand, Addis has found that there is no appreciable difference in the coagulation of blood from deep and superficial punctures. In eight comparative observations the average time from deep punctures was eight minutes, eight seconds, and from superficial punctures, eight minutes, four seconds. It has been my experience also, that, provided the puncture is fairly good and made with a sharp, lance-pointed instrument, it introduces no element of error.

4 *Rate of the Flow*—The rate of flow of blood from the wound, provided it is fairly free, does not affect the clotting-time, according to my experience. Addis, however, states that the rate of flow has proved to be of importance in so far as it affects the time during which the blood is exposed to the air before its introduction into the apparatus. He believes air to have a marked influence on coagulation; its temperature is variable, and dust particles no doubt attach themselves to the drop to a variable extent during its exposure to the air. In a more recent article he states that the amount of thrombokinase, which is one of the most important factors determining the coagulation-time in the blood flowing from a wound, is mainly determined by the length of time during which it has been in contact with the exposed tissues in the wound. Too long contact with the skin, according to Hinman and Sladen, is the element of error in a slow and scanty flow. In one of their cases there was a clotting-time of twenty-three and one-half minutes when there was a freely-flowing hemorrhage and eighteen and three-quarters minutes when

the flow from a second puncture was scanty. At another time with free rapid flow, the time was twenty-two minutes, with comparatively slow flow, fifteen minutes. Murphy and Gould, as mentioned before, attribute the longer coagulation when the flow is free to a washing away of the ferment. As a rule the rate of flow depends on the depth of the puncture.

*5 Pressure on the Part*—Pressure on the parts in expressing the blood introduces a factor of some importance in proportion to the degree of pressure exerted. In ten normal persons blood obtained without any pressure and tested with my coagulometer clotted in eight and seven-tenth minutes. In six cases in which but slight pressure was exerted the coagulation-time was seven and one-half minutes, and in four instances in which the pressure was more marked the time was six minutes. The same was true of tuberculous patients (whose average clotting-time in 100 cases was five and one-sixth minutes). The average coagulation-time of ten patients with no pressure was six and one-eighth minutes, of twenty patients with slight pressure four and seven-eighths minutes, of twenty-six patients with greater pressure four and one-quarter minutes. In no case was much pressure exerted.

Wright, Milhan, and Pratt also found the clotting-time shortened by pressure on the tissues, Wright attributing it to the driving of lymph into a bleeding wound. Addis, on the contrary, was not able to find that pressure makes any appreciable difference, the average time he obtained with pressure being eight minutes, five seconds, and without pressure eight minutes, four and three-quarter seconds.

*6 Stage of the Hemorrhage*—That the last-drawn blood clots more quickly than that drawn first is stated by Hewson, Nasse, Brucke, Ailoin, von der Velden, Cohnheim, Arthus, Bezangon and Labbé, Pratt, and Addis. This refers to both large and small hemorrhages, being more marked in the former. Milhan, and Hinman and Sladen state that drops at the beginning or end of a hemorrhage clot more rapidly than those in the middle, the last believes this to be due to the different rate of flow, an evidence of the influence of skin contact.

Addis was able to demonstrate that a rapid and progressive diminution of the coagulation-time occurs as the hemorrhage continues. Thus the first blood to appear from a wound clotted in seven minutes, fifteen seconds, blood flowing from the wound after one minute in five minutes, fifteen seconds, after two minutes in three minutes, forty seconds. He attributes this change to the influence of fibrin ferment in the wound. Pratt, however, found that a second drop of blood obtained from a cut after the first has coagulated always coagulates more rapidly than the first, even when the skin, after the removal of the first drop, is cleaned carefully with water, alcohol, and ether. Rudolf similarly found that at 20 C the blood from the first drop coagulated in nine minutes, and that

from the same wound two minutes later in five minutes and forty-five seconds, the wound having been carefully wiped dry and clean before the second drop was taken. On another occasion, under similar circumstances, the respective readings were eight and five minutes for the first and second drops at a two-minute interval.

*7 Congestion of the Part Punctured*—Several observers, in objecting to constricting the finger before drawing blood from it, state that congestion of the part from which the blood is obtained leads to diminution in the clotting-time, the explanation being that a greater quantity of coagulation-accelerating substances from the tissues is added to the blood. Wright states that venous congestion by ligatures increases coagulability, believing it due to the effect of carbon dioxide.

Addis found no such change. He produced a very marked congestion in one arm by the application of a Bier's bandage above the elbow. The average of twelve comparative estimations of the clotting-time of blood taken from the congested fingers was eight minutes, two seconds, while the average time of blood taken from the uncongested fingers was seven minutes, fifty-one seconds.

#### 4. INTRINSIC FACTORS, PROBABLY AFFECTING THE BLOOD WITHIN THE VESSELS

In addition to errors in technic that affect the clotting-time of drawn blood, there are probably other factors that may influence the coagulability of the blood while still in the vessels. These include external influences, conditions of the body, normal and pathological, and substances introduced into the body from without.

##### I EXTERNAL CONDITIONS (METEOROLOGICAL)

In many instances I made note of the meteorological conditions existing at the time the test was made, including temperature, barometric pressure, humidity and sunshine.

*1 Outside Temperature*—The clotting-time apparently does not vary with the outside temperature. I noted the outside temperature when making many of my tests, and have grouped the normal and non-tuberculous and also the tuberculous cases according to whether the outside temperature on the day of the test was above or below 75 F, and in the tuberculous cases also above or below 80 F.

It was noted by Robertson and his assistants that the temperature and humidity of the atmosphere influenced the coagulation-time noticeably and uniformly, a hot day with heavy atmosphere causing the coagulation-time to shorten, while a cool day had the opposite effect. Before I had compiled my figures I had the same impression, and thought that possibly



the low average time of the 100 cases of tuberculosis I examined (five and one-sixth minutes) might have been due in part to the fact that most of the tests were made during the hot months of July and August

TABLE 3—CLOTTING-TIME AT DIFFERENT TEMPERATURES

(Obtained with author's coagulometer)

	Normal and Non-Tuberculous Cases at a Temperature of		—Cases of Tuberculosis at— Temperatures of			
	75° F and Above	Below 75° F	80° F and Above	Below 80° F	Above 75° F	75° F and Below
Number of cases	14	25	55	45	81	19
Number of observations	14	30	72	57	99	28
Av clotting-time (minutes)	8	7 $\frac{7}{8}$	5 $\frac{1}{7}$	5 $\frac{1}{4}$	5 $\frac{2}{5}$	5
Max clotting-time (minutes)	12 $\frac{1}{4}$	12 $\frac{1}{4}$	10 $\frac{3}{8}$	10 $\frac{3}{8}$	10 $\frac{3}{8}$	7 $\frac{7}{8}$
Min clotting-time (minutes)	4 $\frac{5}{8}$	3 $\frac{1}{2}$	2 $\frac{1}{4}$	2 $\frac{1}{8}$	2 $\frac{1}{4}$	2 $\frac{1}{8}$

2 *Humidity*—There is apparently no definite relationship between the humidity and the clotting-time. I made note of the humidity on the day of the test, but found it exercised very little influence. The results, in fact, were slightly at variance in thirty-nine normal and non-tuberculous cases and in ninety-seven tuberculous cases.

TABLE 4—CLOTTING-TIME AT DIFFERENT DEGREES OF HUMIDITY

	Normal and Non-Tuberculous Cases With a Humidity of		—Tuberculous Cases With a— Humidity of			
	75 and Above	Below 75	75 and Above	Below 75	70 and Above	Below 70
No of cases	19	20	33	64	55	11
No of observations	21	23	39	86	71	55
Av clotting-time (minutes)	7 $\frac{4}{5}$	8	5 $\frac{1}{2}$	5	5 $\frac{1}{2}$	1 $\frac{7}{8}$
Max clotting-time (minutes)	12 $\frac{1}{4}$	12 $\frac{1}{4}$	10 $\frac{1}{2}$	10 $\frac{3}{8}$	10 $\frac{3}{8}$	10 $\frac{3}{8}$
Min clotting-time (minutes)	4	3 $\frac{1}{2}$	2 $\frac{1}{4}$	2 $\frac{1}{8}$	2 $\frac{1}{4}$	2 $\frac{1}{8}$

Robertson and his assistants, as mentioned above, thought that humidity did affect the clotting-time

3 *Barometric Pressure*—The clotting-time in normal and non-tuberculous individuals seemed to be influenced by the barometric pressure, being shorter by two minutes when the barometric pressure was below 30.1 than when it was 30.1 or above. In the tuberculous cases, however, no difference was observed.

TABLE 5—CLOTTING-TIME AT DIFFERENT BAROMETER PRESSURES

	Non-Tuberculous Cases, at a Barometric Pressure of		Tuberculous Cases, at a Barometric Pressure of	
	30.1 and Above	Below 30.1	30.1 and Above	Below 30.1
No of cases	30	14	11	56
No of observations	30	18	52	74
Aver clotting-time (minutes)	8 $\frac{7}{8}$	6 $\frac{1}{2}$	5 $\frac{1}{2}$	5
Max clotting time (minutes)	12 $\frac{1}{4}$	10 $\frac{1}{2}$	10	10
Min clotting time (minutes)	3 $\frac{1}{2}$	3 $\frac{7}{8}$	2 $\frac{1}{8}$	2 $\frac{1}{4}$

4 *Amount of Sunshine*—Note was made of the number of hours of sunshine on the day of the test in ninety-seven cases of tuberculosis. On the days when there were more than eleven hours of sunshine the clotting-time was half a minute longer than on days when the hours of sunshine were eleven or less.

TABLE 6—RELATION OF THE CLOTTING-TIME TO THE AMOUNT OF SUNSHINE

	Cases of Tuberculosis—	
	11 Hours of Sunshine or Less	Over 11 Hours of Sunshine
Number of cases	45	52
No of observations	52	72
Aver clotting-time (minutes)	5 $\frac{3}{8}$	4 $\frac{9}{10}$
Max clotting-time (minutes)	10 $\frac{3}{8}$	7 $\frac{3}{4}$
Min clotting-time (minutes)	2 $\frac{1}{8}$	2 $\frac{1}{4}$

## II CONDITIONS AFFECTING THE BLOOD ITSELF

There are a number of conditions within the body itself that exert some influence on the clotting-time. Several affect the blood directly, while others have an effect on the body as a whole.

1 *Viscosity*—Buckmaster states that the viscosity of the blood as determined by Hürthle for animals and Hirsch and Buck for man, is found to be inversely related to the coagulation-time, and that the less the viscosity the greater the time. In Addis' cases, however, no relation appeared to exist between the viscosity of the blood and its coagulation-time. Delayed, normal and accelerated coagulation-times were all observed in different cases where there was undoubtedly an increase or decrease of viscosity. Addis thinks the belief that there is a connection between viscosity and coagulation is due to the fact that, unless special precautions are taken, when the blood has an increased viscosity, it takes a longer time than usual to flow from a wound, and takes up more thrombokinase, and so gives a shorter time than normal blood or blood in which the viscosity is low. In my own cases the clotting-time was longer in the viscid than in the non-viscid drops, as may be seen from Table 7.

TABLE 7—RELATION OF THE CLOTTING-TIME TO THE VISCOSITY

	Normal Cases—		Tuberculous Cases—	
	Viscid	Not Viscid	Viscid	Not Viscid
Number of cases	8	5	35	21
Number of observations	8	5	37	22
Aver clotting-time (minutes)	10	8 $\frac{3}{8}$	5 $\frac{3}{8}$	5 $\frac{1}{4}$

This longer clotting-time of viscid drops may be due to the fact that viscid drops are deeper or higher than drops of low viscosity having the same diameters, and consequently contain more blood. The drop of low viscosity, being shallow, is therefore more likely to evaporate and to become dry around the edges than the more viscid and consequently

higher drop That there is a marked difference between the clotting-times of high and shallow drops, amounting to one and three-quarter minutes, Table 8 shows

TABLE 8—RELATION OF HEIGHT OF DROP TO CLOTTING- TIME

Cases of Tuberculosis	High Drops	Shallow Drops
No of cases	35	15
No of observations	36	15
Aver clotting-time (minutes)	5¾	4

It was my experience, moreover, that a viscid drop when tilted may sometimes retain its convex shape before it is completely coagulated. Consequently in Milian's method and its modifications a high degree of viscosity may constitute a source of error. It also has seemed to me that viscid blood sticks to glass better than does thin blood. Should this be the case, viscosity may interfere to some extent with the accuracy of some of the instruments used, such as those of the Brodie-Russell type and particularly those employing capillary tubes.

According to Coleman, altered viscosity may introduce a fallacy in the Brodie-Russell instrument that is difficult to remove. When there is a considerable diminution of the surface tension of the blood, the size of the pendulous drop is much less and therefore the blood is exposed to a relatively large surface of glass, and consequently the observed coagulation-time is unduly shortened.

In my tests the viscosity was judged as being high or low in accordance with the appearance or behavior of the drop. A series of comparative observations on cases in which the viscosity is accurately measured with an instrument of precision might prove of value.

2 *Blood-Pressure*—Hartman states that a variable blood-pressure has no influence on the clotting-time.

3 *Agglutination*—In healthy persons variations in the agglutination of red blood-cells are slight, according to Addis, and have never given rise to serious error or difficulty in tests made with his modification of the Brodie-Russell instrument. In disease the agglutination of corpuscles is greatly increased and in some convalescents it is present in varying degree, preventing estimation of the coagulation-time with his instrument in many cases.

4 *Hemoglobin*—The amount of hemoglobin apparently has no relation to the clotting-time. Of twenty-three cases of anemia I tested with Wright's coagulometer at 37 C, sixteen with between 50 and 75 per cent of hemoglobin had an average clotting-time of two and one-half minutes (normal) and five with hemoglobin below 50 per cent had an average time of two and five-sevenths minutes. Schwab also states that no relation exists between coagulation and hemoglobin, an exsanguinated patient with carcinoma, with scarcely 10 per cent hemoglobin, having the same clotting-time as another person with 70 or 90 per cent.

5 *Leukocytes*—It is the view of many that a high leukocytosis increases coagulation. Stessano and Billon attempt to show by experiments that the blood's content of fibrin ferment is in proportion to the number of leukocytes it contains. Arthus and Milhan both regard fibrin ferment as the product of the secretion of the white blood-cells. Stessano has advanced the hypothesis that of the different kinds of leukocytes the mononuclears are more particularly concerned in caring for the elaboration of fibrin ferment. He thinks, moreover, that the fact that lymph coagulates spontaneously proves that the mononuclear leukocytes, which are the only elements normally figuring in lymph, are well capable of setting free fibrin ferment. In Addis' cases, on the other hand, no evidence was obtained of any connection between leukocytosis and coagulability. All varieties of coagulability were seen, in cases both with and without leukocytosis.

Duncan says too that in cases of high leukocytosis, as in pneumonia, he could not determine that the coagulation-time was hastened. According to Coleman, however, when leukocytosis occurs, either as the result of some pathological condition or of the hypodermic injection of a drug, lengthening of the clotting-time of the blood accompanies it.

No definite relationship could be made out in my cases between the clotting-time and the total number of leukocytes or of the number of mononuclear cells. In thirty-three cases (excluding those of pneumonia) in which the clotting-time was two and one-half minutes, or longer, as determined with Wright's coagulometer at 37 C, the average number of leukocytes was 8,671. In forty-three cases (excluding pneumonia) in which the clotting-time was less than two minutes, the leukocytes averaged 8,176. Adding two cases of pneumonia to the former group and fifteen cases of pneumonia to the latter group brings the average number of leukocytes in these groups up to 8,994 and 14,017 respectively. In one case of pneumonia the clotting-time was estimated six times during the course of the disease. The average clotting-time of the first three examinations, made when the leukocytes averaged 50,653, was two minutes, ten seconds, the average time of the last three, made when the leukocytes averaged 9,286, was one minute, thirty-five seconds.

Differential counts were made in only four cases. Blood containing 14 per cent of mononuclear cells clotted in two minutes, that with 35 per cent in two minutes and a quarter, that with 37 per cent in two minutes and a half, and blood with 39 per cent in three minutes and three-quarters. I would not generalize from these figures that the greater the number of leukocytes as a whole, and of mononuclear cells in particular, the longer is the coagulation-time, but incline rather to the opinion that they bear no relationship to one another.

6 *Bleeding-Time*—Duke determines the bleeding-time by blotting up on absorbent paper at half-minute intervals the blood from a small cut in the lobe of the ear, the rate of decrease in the size of the series of blots—each of which represents one-half minute's outflow of blood—showing the rate of decrease of the hemorrhage. The total duration of such a hemorrhage is called the bleeding-time. Duke states that the bleeding-time is independent of the coagulation-time.

### III NORMAL CONDITIONS AFFECTING THE BODY AS A WHOLE

1 *Age*—Hartman believes that the influence of age on the clotting-time is imaginary. He investigated the blood of women and girls of all ages, 16 to 74 years, and always found the clotting-time four minutes and a half, with occasionally four and five minutes, but never observed a dependence of the clotting-time on age in the diseases he investigated. The age of the individual seems to Rudolf also to make little or no difference in the time of coagulation. At 20 C the average time of children under 12 examined was 8.04 minutes, and of adults 7.72 minutes.

Weiss, using Wright's tubes, observed that the blood in fifty-four healthy adults coagulated in between two and one-quarter minutes and two and three-quarters minutes. Of fifty-eight healthy new-born infants the blood clotted in from two and a half to three and a half minutes in those breast-fed, and in from one and a half to two and a half minutes in those fed artificially.

2 *Sex*—According to Rudolf sex has no evident effect, the average time of females he examined being 7.54 minutes and of males 7.76 minutes.

3 *Time of Day*—A number of observers have noted a diurnal variation in the clotting-time. Vierordt made five observations on himself over a period of fifty-six days, obtaining a different average clotting-time for each time of day, the longest being between 1.15 p. m., the shortest between 7 and 8 p. m. Hinman and Sladen took independent observations on themselves every hour, working apart and using different coagulometers. The longest time for both occurred at about 9 a. m., the fall from this being gradual until the shortest time during the day was reached at 4 p. m. After this the course for both was the same—a gradual rise. Buiker for three days tested his blood every two hours from 6 a. m. to 10 p. m., arriving at the conclusion that the coagulation-time is longest in the morning and usually diminishes until 3 p. m., after which it usually rises again.

Hartman's last 270 estimations seemed at first to bear out Buiker's hypothesis that a shortening of the clotting-time exists in the early afternoon hours. Most of the tests made in the late morning and early afternoon, however, were found to be on women after 6 p. m.

tion, which explained the shortening of the clotting-time. Further examination of the last 100 tests disclosed that all the cases of shortening of the clotting-time occurred after operation, while women not operated on between 1 and 4 p. m. did not experience this shortening of coagulation. Hartman therefore concludes that in his material a physiological daily fluctuation was not observed.

Addis noticed that the more temperature variation was excluded the smaller was the amount of difference in the clotting-times, and that fluctuations in the coagulation curves which he formerly had considered as indicative of intrinsic changes in coagulability, were really due to variations in the surrounding temperature. When the temperature variations were entirely excluded, the coagulation-time was found to be remarkably constant at all times of day and night. Slight variations which occur are irregular and due, he believes, to experimental error. For twenty days Addis took the coagulation-time of his own blood and that of certain other persons every hour or two, and in no one of the charts prepared from these observations do any variations occur which are outside the limit of experimental error.

Rudolf made about 500 estimations of the clotting-time, the results under the same circumstances being constant, but encountered no definite variations at different times of the day. He refers to the fact that, generally speaking, a room will probably be colder in the morning than it will be later in the day, and believes that in any conclusions drawn from experiments in which the temperature of the tubes has not been accurately maintained at the same level, the conclusion would tend to be that the coagulation-time was slower in the morning.

4 *Food*—Vierordt refers to an acceleration of blood-coagulation in the hungry. Coleman observed that the longest coagulation-time occurs one hour after the principal meal of the day, the blood becoming less coagulable as absorption becomes established after a meal. Conversely, the shortest time was recorded when the subject was fasting before breakfast. A slight slowing of coagulation about two hours after a meal was noted by Rudolf.

The above accords with my own experience. Of my normal subjects six that were examined with my method before meal-time gave an average clotting-time of seven and one-sixth minutes, while seventeen examined after a meal gave an average time of nine minutes. This would seem to indicate the possibility at least that the coagulation-time is longer after a meal than before it.

Wright, on the contrary, states that restriction of food diminishes coagulability and therefore advocates the abandoning of starvation in cases of aneurysm unless the coagulometer shows improvement.

Mercier in a large number of observations found the clotting-time shortly after a meal constantly less than shortly before a meal.

Addis estimated the clotting-time on ten different occasions both before and after breakfast, obtaining an average time before food of seven minutes, forty-seven seconds, and an average time after food of seven minutes, forty-six seconds. Hartman also proved by tests before and after full meals that the taking of food does not produce variations of the clotting-time.

5 *Fluids*—According to Wright, restriction of fluid increases coagulability and *vice versa*.

6 *Exercise*—Coleman has demonstrated that there is a certain amount of shortening of the coagulation-time after fifteen or twenty minutes' severe physical exertion. He mentions the possibility of the specific gravity of the blood being slightly increased after loss of fluid from the plasma of perspiration, but as this was not very great during the experiment, he thinks it probable that the slight increase in coagulability was independent of any alteration of the specific gravity.

7 *Menstruation*—A number of circumstances point to a possible connection between menstruation and the clotting-time: the occurrence of vicarious menstruation in the form of nosebleed, etc., the frequent occurrence of hemoptysis at the menstrual period in tuberculous women, and the fact pointed out by Birnbaum and Osten, that menstruating women in many cases bleed remarkably easily and continually at operation, even when the latter is outside of the genital tract, so that some surgeons are unwilling to operate during menstruation. These authors believe that in some way checking of the normal blood-clotting process must accompany the physiological occurrence of menstruation. They found the clotting-time on the average more or less retarded during menstruation. Bode also found retarded coagulation in many menstruating women, though he found it hastened in several cases.

Bell and Hick observed that a very marked drop in the calcium content of the systemic blood always occurs before the menstrual bleeding commences. Often this drop is preceded by a marked rise. Polzl noted a periodical connection between menstruation and the number of red blood-cells in sexually mature women, the highest count usually being one day before the beginning of the bleeding, from which a quick fall follows, which in no way depends on the blood loss.

Cristea and Denk, on the other hand, found the clotting-time of the systemic blood of menstruating women neither shorter nor longer than normal. They also found a normal calcium content in the blood of menstruating women.

Schwab found a normal average clotting of the blood during menstruation. Hartman will only say that with the method he employs he could never find variations from the normal clotting-time.

With my method I tested the coagulation-time in sixteen tuberculous women who were spitting blood. Four, who were menstruating, had an average clotting-time of five and three-quarter minutes. In two cases of amenorrhea at the menstrual period the average clotting-time was also five and three-quarter minutes. The time was five and two-third minutes in ten who were not at the menstrual period, some having passed the menopause. These few cases consequently do not point to any alteration in coagulability at the catamenia.

Hartman regards the uniform clotting-time in women and girls of all ages as settling negatively the question whether an influence is exerted by the circumstance that a woman is at the menstrual age, or has not entered it, or has passed it.

8 *Pregnancy*—Pregnancy probably does not influence the clotting-time. Douglas obtained clotting-times of seven and three-quarter minutes in healthy non-pregnant women and seven and four-tenths minutes in healthy pregnant women. Hartman was not able to determine a deviation from the normal clotting-time during pregnancy, either in the early or in the latter months. Fox made a few observations on women during the latter part of pregnancy which, so far as they go, indicate a tendency to a low coagulation-time, in several cases lower than after delivery.

An increased fibrin content has been noticed by Nasse in the blood of pregnant women.

9 *Puerperium*—Douglas obtained an average clotting-time of seven and three-tenth minutes in normal puerperal women, compared to seven and three-quarters minutes in healthy non-pregnant women. Hingston Fox examined eight puerperal women, all primiparas with normal labors and normal hemorrhage, all suckling their infants. He found the clotting-time immediately after delivery to be below the normal.

(To be continued)



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